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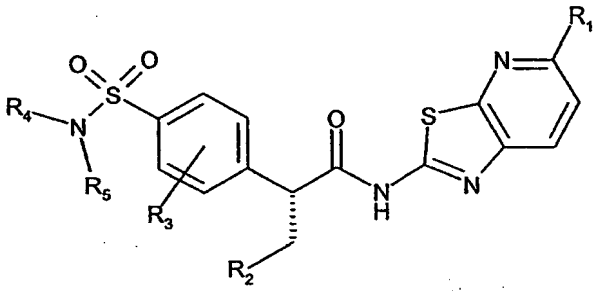
(54) Title: SULFONAMIDE-THIAZOLPYRIDINE DERIVATIVES AS GLUCOKINASE ACTIVATORS USEFUL THE TREATMENT OF TYPE 2 DIABETES



(I)

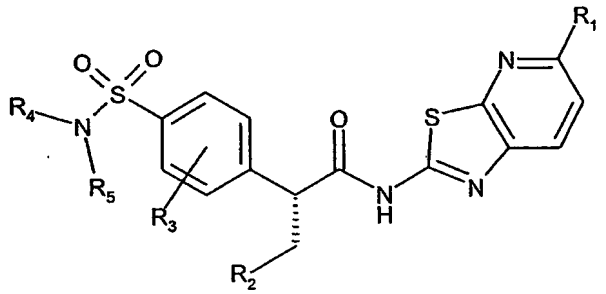
(57) Abstract: The present invention provides compounds of the formula (I), which are activators of glucokinase activity and, thus, may be employed as therapeutic agents for the treatment of glucokinase mediated conditions. Accordingly, the compounds of formula (I) may be employed for the prevention and the treatment of impaired glucose tolerance, Type 2 diabetes and obesity.

SULFONAMIDE-THIAZOLPYRIDINE DERIVATIVES AS GLUCOKINASE ACTIVATORS USEFUL THE TREATMENT OF TYPE 2 DIABETES

Organic Compounds

The present invention relates to thiazolopyridine derivatives, pharmaceutical compositions containing them, and to methods of treating glucokinase mediated conditions, in particular, impaired glucose tolerance and Type 2 diabetes, by employing such compounds.

Accordingly, the present invention provides compounds of the formula



(I)

wherein

R_1 is hydrogen, halogen, cyano, nitro, optionally substituted alkyl, alkoxy, alkylthio, alkylthiono, sulfonyl, carboxy, carbamoyl, sulfamoyl or optionally substituted amino;

R_2 is C_3-C_6 cycloalkyl or C_3-C_6 heterocyclyl;

R_3 is hydrogen, halogen, cyano, lower alkyl or lower alkoxy;

R_4 is hydrogen, optionally substituted alkyl, or cycloalkyl;

R_5 is $-(CR_6R_7)_m$-W-R_8 in which

R_6 and R_7 are independently hydrogen, optionally substituted alkyl or cycloalkyl; or

R_6 and R_7 combined are alkylene which together with the carbon atom to which they are attached form a 3- to 7-membered ring;

m is zero or an integer from 1 to 5;

W is $-NR_9$- in which

R_9 is hydrogen, optionally substituted alkyl or heterocyclyl; or

R_9 is $-C(O)R_{10}$, $-C(O)OR_{10}$, or $-C(O)NR_{10}R_{11}$ in which

R_{10} is optionally substituted alkyl, cycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl;

R_{11} is hydrogen or lower alkyl; or

R_{11} and R_{10} combined are alkylene which together with the nitrogen atom to which they are attached form a 4- to 7-membered ring; or

W is absent;

R_8 is hydrogen, optionally substituted C_1-C_7 alkyl, cycloalkyl, aryl or heterocyclyl; or

R_8 and R_9 combined are alkylene which together with the nitrogen atom to which they are attached form a 4- to 7-membered ring; or

R_5 and R_4 combined are alkylene which together with the nitrogen atom to which they are attached form a 4- to 7-membered ring; or

R_5 and R_4 taken together with the nitrogen atom to which they are attached form a 6- to 12-membered fused, bridged or spiral bicyclic ring, which may be optionally substituted or may contain 1 to 3 other heteroatoms selected from oxygen, nitrogen and sulfur;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

The compounds of the present invention provide pharmacological agents which are glucokinase activators and, thus, may be employed for the treatment of glucokinase mediated conditions. Accordingly, the compounds of formula (I) may be employed for prevention and treatment of impaired glucose tolerance, Type 2 diabetes and obesity.

Listed below are definitions of various terms used to describe the compounds of the present invention. These definitions apply to the terms as they are used throughout the specification unless they are otherwise limited in specific instances either individually or as part of a larger group, e.g., wherein an attachment point of a certain group is limited to a specific atom within that group.

The term "optionally substituted alkyl" refers to unsubstituted or substituted straight- or branched-chain hydrocarbon groups having 1-20 carbon atoms, preferably 1-10 carbon atoms. Exemplary unsubstituted alkyl groups include methyl, ethyl, propyl, isopropyl, *n*-butyl, *t*-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl and the like. Substituted alkyl groups include, but are not limited to, alkyl groups substituted by one or more of the following groups: halo, hydroxy, alkanoyl, alkoxy, alkanoyloxy, thiol, alkylthio, alkylthiono, sulfonyl, sulfamoyl, carbamoyl, cyano, carboxy, acyl, aryl, alkenyl, alkynyl, aralkoxy, guanidino, optionally substituted amino, heterocyclyl including imidazolyl, furyl, thienyl, thiazolyl, pyrrolidyl, pyridyl, pyrimidyl and the like.

The term "lower alkyl" refers to those alkyl groups as described above having 1-7, preferably 2-4 carbon atoms.

The term "halogen" or "halo" refers to fluorine, chlorine, bromine and iodine.

The term "alkenyl" refers to any of the above alkyl groups having at least two carbon atoms and further containing a carbon to carbon double bond at the point of attachment. Groups having 2-4 carbon atoms are preferred.

The term "alkynyl" refers to any of the above alkyl groups having at least two carbon atoms and further containing a carbon to carbon triple bond at the point of attachment. Groups having 2-4 carbon atoms are preferred.

The term "alkylene" refers to a straight-chain bridge of 4-6 carbon atoms connected by single bonds, e.g., $-(CH_2)_X-$, wherein x is 4-6, which may be interrupted with one or more heteroatoms selected from O, S, S(O), $S(O)_2$ or NR, wherein R may be hydrogen, alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl, heteroaralkyl, acyl, carbamoyl, sulfonyl, alkoxycarbonyl, aryloxycarbonyl or aralkoxycarbonyl and the like; and the alkylene may further be substituted with one or more substituents selected from optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, oxo, halogen, hydroxy, carboxy, alkoxy, alkoxycarbonyl and the like.

The term "cycloalkyl" refers to optionally substituted monocyclic, bicyclic or tricyclic hydrocarbon groups of 3-12 carbon atoms, each of which may contain one or more carbon to carbon double bonds, or the cycloalkyl may be substituted by one or more substituents, such as alkyl, halo, oxo, hydroxy, alkoxy, alkanoyl, acylamino, carbamoyl, alkylamino, dialkylamino, thiol, alkylthio, cyano, carboxy, alkoxycarbonyl, sulfonyl, sulfonamido, sulfamoyl, heterocyclyl and the like.

Exemplary monocyclic hydrocarbon groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl and cyclohexenyl and the like.

Exemplary bicyclic hydrocarbon groups include bornyl, indyl, hexahydroindyl, tetrahydronaphthyl, decahydronaphthyl, bicyclo[2.1.1]hexyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.1]heptenyl, 6,6-dimethylbicyclo[3.1.1]heptyl, 2,6,6-trimethylbicyclo[3.1.1]heptyl, bicyclo[2.2.2]octyl and the like.

Exemplary tricyclic hydrocarbon groups include adamantyl and the like.

The term "alkoxy" refers to alkyl-O-.

The term "alkanoyl" refers to alkyl-C(O)-.

The term "alkanoyloxy" refers to alkyl-C(O)-O-.

The terms "alkylamino" and "dialkylamino" refer to alkyl-NH- and $(alkyl)_2N$-, respectively.

The term "alkanoylamino" refers to alkyl-C(O)-NH-.

The term "alkylthio" refers to alkyl-S-.

The term "trialkylsilyl" refers to $(alkyl)_3Si$-.

The term "trialkylsilyloxy" refers to $(alkyl)_3SiO$-.

The term "alkylthiono" refers to alkyl-S(O)-.

The term "alkylsulfonyl" refers to alkyl-$S(O)_2$-.

The term "alkoxycarbonyl" refers to alkyl-O-C(O)-.

The term "alkoxycarbonyloxy" refers to alkyl-O-C(O)O-.

The term "carbamoyl" refers to $H_2NC(O)$-, alkyl-NHC(O)-, $(alkyl)_2NC(O)$-, aryl-NHC(O)-, alkyl(aryl)-NC(O)-, heteroaryl-NHC(O)-, alkyl(heteroaryl)-NC(O)-, aralkyl-NHC(O)-, alkyl(aralkyl)-NC(O)- and the like.

The term "sulfamoyl" refers to $H_2NS(O)_2$-, alkyl-$NHS(O)_2$-, $(alkyl)_2NS(O)_2$-, aryl-$NHS(O)_2$-, alkyl(aryl)-$NS(O)_2$-, $(aryl)_2NS(O)_2$-, heteroaryl-$NHS(O)_2$-, aralkyl-$NHS(O)_2$-, heteroaralkyl-$NHS(O)_2$- and the like.

The term "sulfonamido" refers to alkyl-$S(O)_2$-NH-, aryl-$S(O)_2$-NH-, aralkyl-$S(O)_2$-NH-, heteroaryl-$S(O)_2$-NH-, heteroaralkyl-$S(O)_2$-NH-, alkyl-$S(O)_2$-N(alkyl)-, aryl-$S(O)_2$-N(alkyl)-, aralkyl-$S(O)_2$-N(alkyl)-, heteroaryl-$S(O)_2$-N(alkyl)-, heteroaralkyl-$S(O)_2$-N(alkyl)- and the like.

The term "sulfonyl" refers to alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl and the like.

The term "optionally substituted amino" refers to a primary or secondary amino group which may optionally be substituted by a substituent such as acyl, sulfonyl, alkoxycarbonyl, cycloalkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, carbamoyl and the like.

The term "aryl" refers to monocyclic or bicyclic aromatic hydrocarbon groups having 6-12 carbon atoms in the ring portion, such as phenyl, biphenyl, naphthyl and tetrahydronaphthyl, each of which may optionally be substituted by 1-4 substituents, such as optionally substituted alkyl, trifluoromethyl, cycloalkyl, halo, hydroxy, alkoxy, acyl, alkanoyloxy, aryloxy, optionally substituted amino, thiol, alkylthio, arylthio, nitro, cyano, carboxy, alkoxycarbonyl, carbamoyl, alkylthiono, sulfonyl, sulfonamido, heterocyclyl and the like.

The term "monocyclic aryl" refers to optionally substituted phenyl as described under aryl.

The term "aralkyl" refers to an aryl group bonded directly through an alkyl group, such as benzyl.

The term "aralkanoyl" refers to aralkyl-C(O)-.

The term "aralkylthio" refers to aralkyl-S-.

The term "aralkoxy" refers to an aryl group bonded directly through an alkoxy group.

The term "arylsulfonyl" refers to aryl-$S(O)_2$-.

The term "arylthio" refers to aryl-S-.

The term "aroyl" refers to aryl-C(O)-.

The term "aroyloxy" refers to aryl-C(O)-O-.

The term "aroylamino" refers to aryl-C(O)-NH-.

The term "aryloxycarbonyl" refers to aryl-O-C(O)-.

The term "heterocyclyl" or "heterocyclo" refers to an optionally substituted, fully saturated or unsaturated, aromatic or nonaromatic cyclic group, e.g., which is a 4- to 7-membered monocyclic, 7- to 12-membered bicyclic or 10- to 15-membered tricyclic ring system, which has at least one heteroatom in at least one carbon atom-containing ring. Each ring of the heterocyclic group containing a heteroatom may have 1, 2 or 3 heteroatoms selected from nitrogen atoms, oxygen atoms and sulfur atoms, where the nitrogen and sulfur heteroatoms may also optionally be oxidized. The heterocyclic group may be attached at a heteroatom or a carbon atom.

Exemplary monocyclic heterocyclic groups include pyrrolidinyl, pyrrolyl, pyrazolyl, oxetanyl, pyrazolinyl, imidazolyl, imidazolinyl, imidazolidinyl, triazolyl, oxazolyl, oxazolidinyl, isoxazolinyl, isoxazolyl, thiazolyl, thiadiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, furyl, tetrahydrofuryl, thienyl, oxadiazolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, 4-piperidonyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, tetrahydropyranyl, morpholinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, 1,3-dioxolane and tetrahydro-1,1 -dioxothienyl, 1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl and the like.

Exemplary bicyclic heterocyclic groups include indolyl, dihydroidolyl, benzothiazolyl, benzoxazinyl, benzoxazolyl, benzothienyl, benzothiazinyl, quinuclidinyl, quinolinyl, tetrahydroquinolinyl, decahydroquinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, decahydroisoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzofuryl, chromonyl, coumarinyl, benzopyranyl, cinnolinyl, quinoxalinyl, indazolyl, pyrrolopyridyl, furopyridinyl (such as furo[2,3-c]pyridinyl, furo[3,2-b]-pyridinyl] or furo[2,3-b]pyridinyl), dihydroisoindolyl, 1,3-dioxo-1,3-dihydroisoindol-2-yl, dihydroquinazolinyl (such as 3,4-dihydro-4-oxo-quinazolinyl), phthalazinyl and the like.

Exemplary tricyclic heterocyclic groups include carbazolyl, dibenzoazepinyl, dithienoazepinyl, benzindolyl, phenanthrolinyl, acridinyl, phenanthridinyl, phenoxazinyl, phenothiazinyl, xanthenyl, carbolinyl and the like.

The term "heterocyclyl" includes substituted heterocyclic groups. Substituted heterocyclic groups refer to heterocyclic groups substituted with 1, 2 or 3 substituents selected from the group consisting of the following:

(a) optionally substituted alkyl;
(b) hydroxyl (or protected hydroxyl);
(c) halo;
(d) oxo, i.e., =O;
(e) optionally substituted amino;
(f) alkoxy;
(g) cycloalkyl;
(h) carboxy;
(i) heterocyclooxy;
(j) alkoxycarbonyl, such as unsubstituted lower alkoxycarbonyl;

(k) mercapto;
(l) nitro;
(m) cyano;
(n) sulfamoyl;
(o) alkanoyloxy;
(p) aroyloxy;
(q) arylthio;
(r) aryloxy;
(s) alkylthio;
(t) formyl;
(u) carbamoyl;
(v) aralkyl; and
(w) aryl optionally substituted with alkyl, cycloalkyl, alkoxy, hydroxyl, amino, acylamino, alkylamino, dialkylamino or halo.

The term "heterocyclooxy" denotes a heterocyclic group bonded through an oxygen bridge.

The term "heterocycloalkyl" refers to nonaromatic heterocyclic groups as described above.

The term "heteroaryl" refers to an aromatic heterocycle, e.g., monocyclic or bicyclic aryl, such as pyrrolyl, pyrazolyl, imidazolyl, triazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, furyl, thienyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolyl, benzothiazolyl, benzoxazolyl, benzothienyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzofuryl and the like, optionally substituted by, e.g., lower alkyl, lower alkoxy or halo.

The term "heteroarylsulfonyl" refers to heteroaryl-$S(O)_2$-.

The term "heteroaroyl" refers to heteroaryl-C(O)-.

The term "heteroaroylamino" refers to heteroaryl-C(O)NH-.

The term "heteroaralkyl" refers to a heteroaryl group bonded through an alkyl group.

The term "heteroaralkanoyl" refers to heteroaralkyl-C(O)-.

The term "heteroaralkanoylamino" refers to heteroaralkyl-C(O)NH-.

The term "acyl" refers to alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl and the like.

The term "acylamino" refers to alkanoylamino, aroylamino, heteroaroylamino, aralkanoylamino, heteroaralkanoylamino and the like.

Pharmaceutically acceptable salts of the compounds of the present invention refer to salts formed with acids, namely acid addition salts, such as of mineral acids, organic carboxylic acids and organic sulfonic acids, e.g., hydrochloric acid, maleic acid and methanesulfonic acid, respectively.

Similarly, pharmaceutically acceptable salts of the compounds of the invention refer to salts formed with bases, namely cationic salts, such as alkali and alkaline earth metal salts, e.g., sodium, lithium, potassium, calcium and magnesium, as well as ammonium salts, e.g., ammonium, trimethylammonium, diethylammonium and tris(hydroxymethyl)-methyl-ammonium salts and salts with amino acids provided an acidic group constitutes part of the structure.

As described herein above, the present invention provides thiazolopyridine derivatives of formula (I), pharmaceutical compositions containing them, methods for preparing said compounds, and methods of treating glucokinase mediated conditions by administration of a therapeutically effective amount of a compound of the present invention, or a pharmaceutical composition thereof.

Preferred are the compounds of formula (I) wherein

R_1 is hydrogen, halogen, cyano, nitro, alkoxy, carboxy, carbamoyl or optionally substituted amino;

R_2 is C_3-C_6 cycloalkyl or C_3-C_6 heterocyclyl;

R_3 is hydrogen, halogen, cyano, lower alkyl or lower alkoxy;

R_4 is hydrogen or lower alkyl;

R_5 is $-(CR_6R_7)_m$-W-R_8 in which

R_6 and R_7 are independently hydrogen or optionally substituted lower alkyl;

m is zero or an integer from 1 to 5;

W is $-NR_9-$ in which

R_9 is hydrogen or lower alkyl; or

R_9 is $-C(O)R_{10}$, $-C(O)OR_{10}$, or $-C(O)NR_{10}R_{11}$ in which

R_{10} is optionally substituted alkyl, cycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl;

R_{11} is hydrogen or lower alkyl; or

R_{11} and R_{10} combined are alkylene which together with the nitrogen atom to which they are attached form a 5- to 7-membered ring; or

W is absent;

R_8 is hydrogen, optionally substituted C_1-C_7 alkyl, cycloalkyl, aryl or heterocyclyl; or

R_8 and R_9 combined are alkylene which together with the nitrogen atom to which they are attached form a 5- to 7-membered ring; or

R_5 and R_4 combined are alkylene which together with the nitrogen atom to which they are attached form a 5- to 7-membered ring;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

Futher preferred are the compounds of formula (I) wherein

R_4 is hydrogen or lower alkyl;

R_5 is $-(CR_6R_7)_m$-W-R_8 in which

R_6 and R_7 are independently hydrogen or optionally substituted lower alkyl;

m is an integer from 2 to 5;

W is $-NR_9-$ in which

R_9 is hydrogen or lower alkyl; or

R_9 is $-C(O)R_{10}$, $-C(O)OR_{10}$, or $-C(O)NR_{10}R_{11}$ in which

R_{10} is optionally substituted alkyl, cycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl;

R_{11} is hydrogen or lower alkyl; or

R_{11} and R_{10} combined are alkylene which together with the nitrogen atom to which they are attached form a 5- to 7-membered ring; or

R_8 is hydrogen, optionally substituted C_1-C_7 alkyl, cycloalkyl, aryl or heterocyclyl; or

R_8 and R_9 combined are alkylene which together with the nitrogen atom to which they are attached form a 5- to 7-membered ring;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

More preferred are the compounds of formula (I) wherein

R_1 is hydrogen, halogen,C_1-C_4 alkoxy, carboxy or carbamoyl;

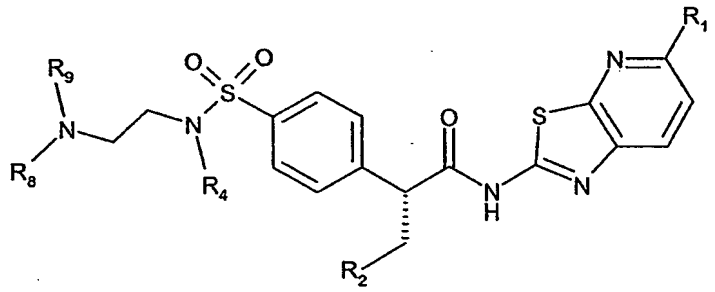
R_2 is C_3-C_5 cycloalkyl;

R_3 is hydrogen;

R_6 and R_7 are hydrogen;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

Most preferred are the compounds of formula (I) having the formula



(IA)

wherein

R_1 is hydrogen, halogen, C_1-C_4 alkoxy, carboxy or carbamoyl;

R_2 is C_3-C_5 cycloalkyl;

R_4 is hydrogen or lower alkyl;

R_8 is hydrogen, optionally substituted C_1-C_7 alkyl, cycloalkyl, aryl or heterocyclyl;

R_9 is hydrogen or lower alkyl; or

R_9 is $-C(O)R_{10}$, $-C(O)OR_{10}$, or $-C(O)NR_{10}R_{11}$ in which

R_{10} is optionally substituted alkyl, cycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl;

R_{11} is hydrogen or lower alkyl; or

R_{11} and R_{10} combined are alkylene which together with the nitrogen atom to which they are attached form a 5- to 7-membered ring; or

R_9 and R_8 combined are alkylene which together with the nitrogen atom to which they are attached form a 5- to 7-membered ring;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

Preferred are the compounds of formula (IA) wherein

R_1 is methoxy;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

Preferred are also the compounds of formula (IA) wherein

R_2 is cyclopentyl;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

Preferred are also the compounds of formula (IA) wherein

R_1 is methoxy;

R_2 is cyclopentyl;

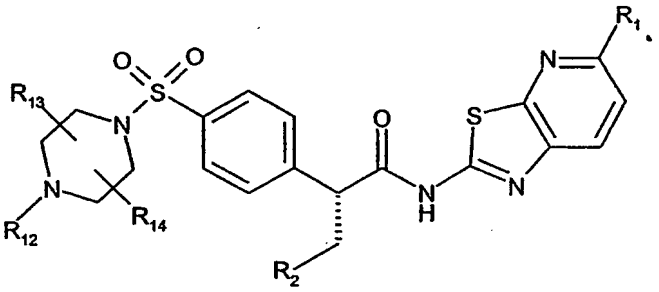
or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

Preferred are also the compounds of formula (I), designated as the A group, wherein

R_4 and R_5 combined are alkylene which together with the nitrogen atom to which they are attached form a 5- to 7-membered ring;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

Preferred are the compounds in the A group of the formula



(IB)

wherein

R_1 is hydrogen, halogen, C_1-C_4 alkoxy, carboxy or carbamoyl;

R_2 is C_3-C_5 cycloalkyl;

R_{12} is hydrogen, optionally substituted lower alkyl, cycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl; or

R_{12} is -C(O)R_{15}, -C(O)OR_{15}, or -C(O)N$R_{15}R_{16}$ in which

R_{15} optionally substituted alkyl, cycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl;

R_{16} is hydrogen or lower alkyl; or

R_{16} and R_{15} combined are alkylene which together with the nitrogen atom to which they are attached form a 5- to 7-membered ring;

R_{13} and R_{14} are independently hydrogen or lower alkyl;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

Preferred are the compounds of formula (IB) wherein

R_1 is methoxy;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

Preferred are also the compounds of formula (IB) wherein

R_2 is cyclopentyl;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

Preferred are also the compounds of formula (IB) wherein

R_1 is methoxy;

R_2 is cyclopentyl;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

Preferred are also the compounds of formula (IB) wherein

R_{12} is methyl;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

Preferred are also the compounds of formula (IB) wherein

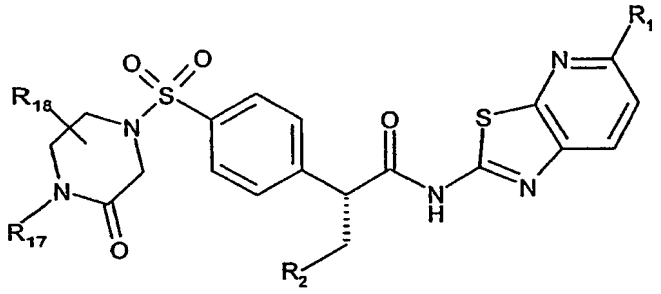
R_1 is methoxy;

R_2 is cyclopentyl;

R_{13} and R_{14} are independently hydrogen or methyl;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

Preferred are also the compounds in the A group of the formula



(IC)

wherein

R_1 is hydrogen, halogen, C_1-C_4 alkoxy, carboxy or carbamoyl;

R_2 is C_3-C_5 cycloalkyl;

R_{17} is hydrogen, optionally substituted lower alkyl, cycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl;

R_{18} is hydrogen or lower alkyl;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

Preferred are the compounds of formula (IC) wherein

R_1 is methoxy;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

Preferred are also the compounds of formula (IC) wherein

R_2 is cyclopentyl;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

Preferred are also the compounds of formula (IC) wherein

R_1 is methoxy;

R_2 is cyclopentyl;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

Preferred are also the compounds of formula (IC) wherein

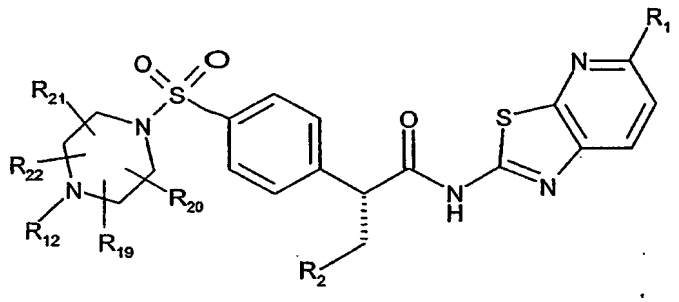
R_1 is methoxy;

R_2 is cyclopentyl;

R_{18} is hydrogen or methyl;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

Preferred are also the compounds in the A group of the formula



(ID)

wherein

R_1 is hydrogen, halogen, C_1-C_4 alkoxy, carboxy or carbamoyl;

R_2 is C_3-C_5 cycloalkyl;

R_{12} is hydrogen, optionally substituted lower alkyl, cycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl; or

R_{12} is -C(O)R_{15}, -C(O)OR_{15}, or -C(O)N$R_{15}R_{16}$ in which

R_{15} optionally substituted alkyl, cycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl;

R_{16} is hydrogen or lower alkyl; or

R_{16} and R_{15} combined are alkylene which together with the nitrogen atom to which they are attached form a 5- to 7-membered ring;

R_{19}, R_{20}, R_{21} and R_{22} are independently hydrogen, optionally substituted lower alkyl, cycloalkyl, aryl or heterocyclyl;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

Preferred are the compounds of formula (ID) wherein

R_1 is methoxy;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

Preferred are also the compounds of formula (ID) wherein

R_2 is cyclopentyl;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

Preferred are also the compounds of formula (ID) wherein

R_1 is methoxy;

R_2 is cyclopentyl;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

Preferred are also the compounds of formula (ID) wherein

R_{12} is methyl;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

Preferred are also the compounds of formula (ID) wherein

R_1 is methoxy;

R_2 is cyclopentyl;

R_{19}, R_{20}, R_{21} and R_{22} are methyl;

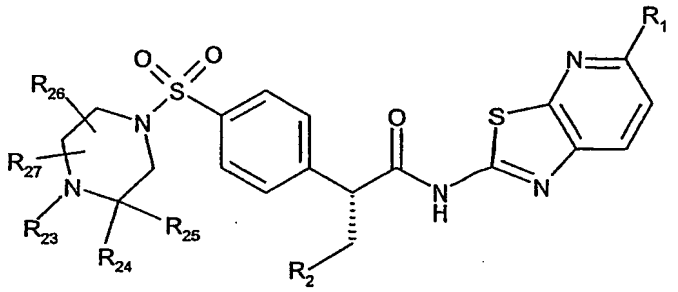
or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

Preferred are also the compounds of formula (I), designated as the B group, wherein

R_4 and R_5 taken together with the nitrogen atom to which they are attached form a 8- to 12-membered fused, bridged or spiral bicyclic ring, which may be optionally substituted or may contain 1 to 3 other heteroatoms selected from oxygen, nitrogen and sulfur;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

Preferred are the compounds in the B group of the formula



(IE)

wherein

R_1 is hydrogen, halogen, C_1-C_4 alkoxy, carboxy or carbamoyl;

R_2 is C_3-C_5 cycloalkyl;

R_{12} is hydrogen, optionally substituted lower alkyl, cycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl; or

R_{23} is $-C(O)R_{15}$, $-C(O)OR_{15}$, or $-C(O)NR_{15}R_{16}$ in which

R_{15} optionally substituted alkyl, cycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl;

R_{16} is hydrogen or lower alkyl; or

R_{16} and R_{15} combined are alkylene which together with the nitrogen atom to which they are attached form a 5- to 7-membered ring; or

R_{23} and R_{24} combined are alkylene which together with the nitrogen and carbon atoms to which they are attached form a 4- to 7-membered ring;

R_{25} is hydrogen; or

R_{25} and R_{24} combined are alkylene which together with the carbon atom to which they are attached form a 3- to 7-membered ring;

R_{26} and R_{27} are independently optionally substituted lower alkyl, cycloalkyl, aryl or heterocyclyl;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

Preferred are the compounds of formula (IE) wherein

R_1 is methoxy;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

Preferred are the compounds of formula (IE) wherein

R_2 is cyclopentyl;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

Preferred are the compounds of formula (IE) wherein

R_1 is methoxy;

R_2 is cyclopentyl;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

The compounds of the invention depending on the nature of the substituents possess one or more asymmetric centers. The resulting diastereoisomers, optical isomers, i.e., enantiomers, and geometric isomers, and mixtures thereof, are encompassed by the instant invention. Preferred are the compounds of the present invention wherein the substituent at the carbon atom adjacent to the amide group attains the *R*-configuration.

Particular embodiments of the invention are:

3-Cyclopentyl-2-(4-cyclopropylsulfamoyl-phenyl)-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-2-[4-(2-methoxy-ethylsulfamoyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-2-[4-(3-methoxy-benzylsulfamoyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-(4-phenylsulfamoyl-phenyl)-propionamide;

2-[4-(2-Carbamoyl-ethylsulfamoyl)-phenyl]-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-2-(4-diisopropylsulfamoyl-phenyl)-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-2-{4-[(furan-2-ylmethyl)-sulfamoyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(phenyl-propyl-sulfamoyl)-phenyl]-propionamide;

3-Cyclopentyl-2-(4-dimethylsulfamoyl-phenyl)-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;
3-Cyclopentyl-2-(4-diethylsulfamoyl-phenyl)-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;
3-Cyclopentyl-2-(4-dipropylsulfamoyl-phenyl)-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;
3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-{4-[(pyridin-3-ylmethyl)-sulfamoyl]-phenyl}-propionamide;
2-(4-Cyclohexylsulfamoyl-phenyl)-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;
3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(piperidine-1-sulfonyl)-phenyl]-propionamide;
3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(morpholine-4-sulfonyl)-phenyl]-propionamide;
3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-{4-[(thiophen-2-ylmethyl)-sulfamoyl]-phenyl}-propionamide;
3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(pyridin-3-ylsulfamoyl)-phenyl]-propionamide;
3-Cyclopentyl-2-[4-(2-fluoro-benzylsulfamoyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;
3-Cyclopentyl-2-[4-(4-methoxy-benzylsulfamoyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;
2-(4-Benzylsulfamoyl-phenyl)-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;
2-[4-(Benzyl-methyl-sulfamoyl)-phenyl]-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;
3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide;
3-Cyclopentyl-2-(4-dibutylsulfamoyl-phenyl)-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;
3-Cyclopentyl-2-[4-(4-ethyl-piperazine-1-sulfonyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;
2-[4-(4-Acetyl-piperazine-1-sulfonyl)-phenyl]-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(piperazine-1-sulfonyl)-phenyl]-propionamide hydrochloride;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(4-phenyl-piperazine-1-sulfonyl)-phenyl]-propionamide;

3-Cyclopentyl-2-{4-[4-(2-methoxy-phenyl)-piperazine-1-sulfonyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

2-{4-[4-(3-Chloro-phenyl)-piperazine-1-sulfonyl]-phenyl}-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

2-[4-(4-Benzyl-piperazine-1-sulfonyl)-phenyl]-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-2-[4-(4-isopropyl-piperazine-1-sulfonyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(4-o-tolyl-piperazine-1-sulfonyl)-phenyl]-propionamide;

N-[2-(2-{4-[4-(2-Chloro-phenyl)-piperazine-1-sulfonyl]-phenyl}-3-cyclopentyl-propionylamino)-thiazol-5-yl]-acetimidic acid methyl ester;

3-Cyclopentyl-2-{4-[4-(4-fluoro-phenyl)-piperazine-1-sulfonyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(4-pyridin-2-yl-piperazine-1-sulfonyl)-phenyl]-propionamide;

3-Cyclopentyl-2-{4-[(2-hydroxy-ethyl)-methyl-sulfamoyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(4-pyridin-4-yl-piperazine-1-sulfonyl)-phenyl]-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(2-piperidin-1-yl-ethylsulfamoyl)-phenyl]-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(2-pyrrolidin-1-yl-ethylsulfamoyl)-phenyl]-propionamide;

3-Cyclopentyl-2-{4-[(2-dimethylamino-ethyl)-ethyl-sulfamoyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide hydrochloride;

3-Cyclopentyl-2-[4-(2-dimethylamino-ethylsulfamoyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide hydrochloride;

3-Cyclopentyl-2-{4-[4-(2-hydroxy-ethyl)-piperazine-1-sulfonyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-{4-[methyl-(2-pyrrolidin-1-yl-ethyl)-sulfamoyl]-phenyl}-propionamide hydrochloride;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-{4-[methyl-(2-piperidin-1-yl-ethyl)-sulfamoyl]-phenyl}-propionamide hydrochloride;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-{4-[methyl-(2-morpholin-4-yl-ethyl)-sulfamoyl]-phenyl}-propionamide;

4-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-piperazin-1-yl)-acetic acid ethyl ester;

3-Cyclopentyl-2-{4-[(2-diethylamino-ethyl)-methyl-sulfamoyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-2-[4-(2-hydroxy-ethylsulfamoyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

2-[4-(4-Carbamoylmethyl-piperazine-1-sulfonyl)-phenyl]-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(pyrrolidine-1-sulfonyl)-phenyl]-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(pyridin-2-ylsulfamoyl)-phenyl]-propionamide;

4-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonylamino}-piperidine-1-carboxylic acid tert-butyl ester;

4-({4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonylamino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester;

3-Cyclopentyl-2-{4-[(1-ethyl-pyrrolidin-2-ylmethyl)-sulfamoyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(piperidin-4-ylsulfamoyl)-phenyl]-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-{4-[(piperidin-4-ylmethyl)-sulfamoyl]-phenyl}-propionamide;

(4-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-piperazin-1-yl)-acetic acid ethyl ester;

3-Cyclopentyl-2-{4-[(3-hydroxy-5-hydroxymethyl-2-methyl-pyridin-4-ylmethyl)-sulfamoyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonylamino}-azetidine-1-carboxylic acid tert-butyl ester;

(1-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-azetidin-3-yl)-carbamic acid tert-butyl ester;

3-({4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonylamino}-methyl)-azetidine-1-carboxylic acid tert-butyl ester;

1-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-pyrrolidine-2-carboxylic acid;

2-[4-(Azetidin-3-ylsulfamoyl)-phenyl]-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

2-[4-(3-Amino-azetidine-1-sulfonyl)-phenyl]-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

2-{4-[(Azetidin-3-ylmethyl)-sulfamoyl]-phenyl}-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-(4-sulfamoyl-phenyl)-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-{4-[(pyridin-4-ylmethyl)-sulfamoyl]-phenyl}-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-{4-[(pyridin-2-ylmethyl)-sulfamoyl]-phenyl}-propionamide;

4-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonylamino}-benzoic acid;

3-Cyclopentyl-2-[4-(4-dimethylamino-phenylsulfamoyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

2-[4-(4-Cyclohexylmethyl-piperazine-1-sulfonyl)-phenyl]-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(1,2,2,6,6-pentamethyl-piperidin-4-ylsulfamoyl)-phenyl]-propionamide;

3-Cyclopentyl-2-[4-(1,1-dimethyl-2-morpholin-4-yl-ethylsulfamoyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

(S)-3-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin–2-ylcarbamoyl)-ethyl]-benzenesulfonylamino}-piperidine-1-carboxylic acid tert-butyl ester;

2-[4-([1,4']Bipiperidinyl-1'-sulfonyl)-phenyl]-3-cyclopentyl-N–(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-2-[4-(4-diethylamino-piperidine-1-sulfonyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(4-pyrrolidin-1-yl-piperidine-1-sulfonyl)-phenyl]-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(octahydro-pyrido[1,2-a]pyrazine-2-sulfonyl)-phenyl]-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(pyridin-4-ylsulfamoyl)-phenyl]-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-((S)-piperidin-3-ylsulfamoyl)-phenyl]-propionamide;

3-Cyclopentyl-2-[4-(1-ethyl-piperidin-3-ylsulfamoyl)-phenyl]–N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

2-{4-[4-(2-Cyano-ethyl)-piperazine-1-sulfonyl]-phenyl}-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(4-piperidin-1-ylmethyl-phenylsulfamoyl)-phenyl]-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(1-phenyl-2-pyrrolidin-1-yl-ethylsulfamoyl)-phenyl]-propionamide;

2-[4-(4-Cyclohexyl-piperazine-1-sulfonyl)-phenyl]-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-2-[4-(2-dimethylamino-2-pyridin-3-yl-ethylsulfamoyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-{4-[methyl-(1-methyl-piperidin-4-yl)-sulfamoyl]-phenyl}-propionamide;

2-[4-(4-Cyclooctyl-piperazine-1-sulfonyl)-phenyl]-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(4-phenethyl-piperazine-1-sulfonyl)-phenyl]-propionamide;

(R)-3-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonylamino}-piperidine-1-carboxylic acid tert-butyl ester;

3-Cyclopentyl-2-{4-[4-(2-ethoxy-ethyl)-piperazine-1-sulfonyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-2-{4-[4-(2-diethylamino-ethyl)-piperazine-1-sulfonyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-((R)-piperidin-3-ylsulfamoyl)-phenyl]-propionamide;

(1-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-azetidin-3-ylamino)-acetic acid ethyl ester;

[3-({4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonylamino}-methyl)-azetidin-1-yl]-acetic acid ethyl ester;

3-Cyclopentyl-2-[4-(hexahydro-pyrrolo[1,2-a]pyrazine-2-sulfonyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

4-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonylamino}-piperidine-1-carboxylic acid ethyl ester;

3-Cyclopentyl-2-{4-[cyclopropyl-(1-methyl-piperidin-4-yl)-sulfamoyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

2-[4-(4-Benzyl-4,7-diaza-spiro[2.5]octane-7-sulfonyl)-phenyl]-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-{4-[4-(4-methyl-piperazin-1-yl)-piperidine-1-sulfonyl]-phenyl}-propionamide;

3-Cyclopentyl-2-[4-(4-cyclopentyl-piperazine-1-sulfonyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-2-[4-(4,7-diaza-spiro[2.5]octane-7-sulfonyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-({4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonylamino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester;

(S)-1-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-pyrrolidine-2-carboxylic acid;

(R)-1-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-pyrrolidine-2-carboxylic acid;

3-Cyclopentyl-2-{4-[4-(2-diethylamino-acetyl)-piperazine-1-sulfonyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-{4-[(piperidin-3-ylmethyl)-sulfamoyl]-phenyl}-propionamide;

2-(4-Butyrylsulfamoyl-phenyl)-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

2-[4-(4-Cyanomethyl-piperazine-1-sulfonyl)-phenyl]-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonylamino}-propionic acid ethyl ester;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-{4-[methyl-(1-methyl-1H-imidazol-2-ylmethyl)-sulfamoyl]-phenyl}-propionamide;

3-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonylamino}-propionic acid;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-{4-[3-(4-methyl-piperazin-1-yl)-3-oxo-propylsulfamoyl]-phenyl}-propionamide;

3-Cyclopentyl-2-{4-[2-(4-hydroxy-piperidin-1-yl)-ethylsulfamoyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

2-[4-(4-Cyclobutyl-piperazine-1-sulfonyl)-phenyl]-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

2-[4-(4-Allyl-piperazine-1-sulfonyl)-phenyl]-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

(1-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-azetidin-3-ylamino)-acetic acid;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(2-piperidin-1-ylmethyl-phenylsulfamoyl)-phenyl]-propionamide;

3-Cyclopentyl-2-{4-[4-(2-dimethylamino-ethyl)-phenylsulfamoyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-(4-propionylsulfamoyl-phenyl)-propionamide;

[3-({4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonylamino}-methyl)-azetidin-1-yl]-acetic acid;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-{4-[4-(2,2,2-trifluoro-acetyl)-piperazine-1-sulfonyl]-phenyl}-propionamide;

3-Cyclopentyl-2-[4-(3-isopropylamino-azetidine-1-sulfonyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-2-[4-(1-isopropyl-azetidin-3-ylsulfamoyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-2-{4-[(1-isopropyl-azetidin-3-ylmethyl)-sulfamoyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-{4-[(oxazol-2-ylmethyl)-sulfamoyl]-phenyl}-propionamide;

3-Cyclopentyl-2-{4-[4-(2-methanesulfonyl-ethyl)-piperazine-1-sulfonyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

2-{4-[4-(3-Cyano-propyl)-piperazine-1-sulfonyl]-phenyl}-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(tetrahydro-pyran-4-ylsulfamoyl)-phenyl]-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-{4-[1-(tetrahydro-pyran-4-yl)-azetidin-3-ylsulfamoyl]-phenyl}-propionamide;

4-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-3-hydroxymethyl-piperazine-1-carboxylic acid tert-butyl ester;

(S)-2-tert-Butoxycarbonylamino-4-{4-[2-cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonylamino}-butyric acid tert-butyl ester;

S)-2-Amino-4-{4-[2-cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonylamino}-butyric acid;

3-Cyclopentyl-2-{4-[4-(2-imidazol-1-yl-ethyl)-piperazine-1-sulfonyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-2-[4-(2-hydroxymethyl-piperazine-1-sulfonyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

(4-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-piperazin-1-yl)-acetic acid;

3-Cyclopentyl-2-{4-[(2-methoxy-ethyl)-(1-methyl-piperidin-4-yl)-sulfamoyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-2-{4-[(2-methoxy-ethyl)-pyridin-2-ylmethyl-sulfamoyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide hydrochloride;

3-Cyclopentyl-2-{4-[(2-hydroxy-ethyl)-(1-methyl-piperidin-4-yl)-sulfamoyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

2-[4-(4-Benzooxazol-2-yl-piperazine-1-sulfonyl)-phenyl]-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-2-[4-(furan-2-ylmethyl-methyl-sulfamoyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-2-[4-(3-hydroxy-4,7-dihydro-5H-isoxazolo[5,4-c]pyridine-6-sulfonyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

2-[4-((S)-1-Benzyl-piperidin-3-ylsulfamoyl)-phenyl]-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-{4-[4-(2,2,2-trifluoro-ethyl)-piperazine-1-sulfonyl]-phenyl}-propionamide;

({4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-pyridin-2-ylmethyl-amino)-acetic acid ethyl ester hydrochloride;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(4-pyridin-3-ylmethyl-piperazine-1-sulfonyl)-phenyl]-propionamide hydrochloride;

1'-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-[1,4']bipiperidinyl-4-carboxylic acid ethyl ester hydrochloride;

1'-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-[1,4']bipiperidinyl-4-carboxylic acid hydrochloride;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-{4-[2-(1-methyl-pyrrolidin-2-yl)-ethylsulfamoyl]-phenyl}-propionamide;

({4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-pyridin-2-ylmethyl-amino)-acetic acid;

3-({4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-furan-2-ylmethyl-amino)-propionic acid ethyl ester;

2-{4-[(2-Cyano-ethyl)-furan-2-ylmethyl-sulfamoyl]-phenyl}-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-2-{4-[(3-methoxy-propyl)-(1-methyl-piperidin-4-yl)-sulfamoyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-2-{4-[(2-diethylamino-ethyl)-(1-methyl-piperidin-4-yl)-sulfamoyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-2-{4-[(3-diethylamino-propyl)-(1-methyl-piperidin-4-yl)-sulfamoyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-({4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-furan-2-ylmethyl-amino)-propionic acid;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(3-phenyl-piperazine-1-sulfonyl)-phenyl]-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(3,3,4-trimethyl-piperazine-1-sulfonyl)-phenyl]-propionamide;

3-Cyclopentyl-2-[4-(3,3-dimethyl-piperazine-1-sulfonyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

4-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-piperazine-1,3-dicarboxylic acid 1-tert-butyl ester;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(4-methyl-3-phenyl-piperazine-1-sulfonyl)-phenyl]-propionamide; and

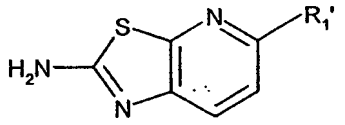
3-Cyclopentyl-2-[4-(2,5-diaza-bicyclo[2.2.1]heptane-2-sulfonyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

Compounds of formula (I) may be prepared using methods well known in the art, e.g., according to Method A or Method B as outlined herein below.

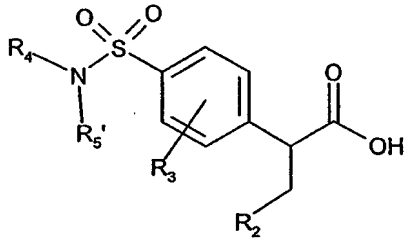
Method A:

Compounds of formula (I) may be obtained by coupling an amine of the formula



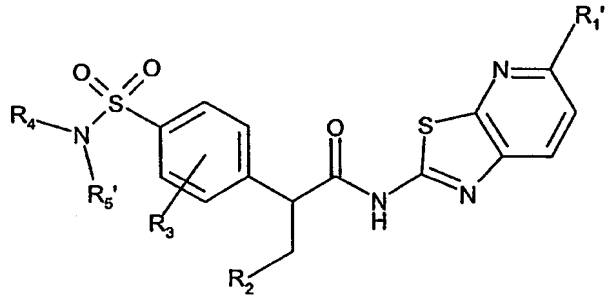
(II),

or acid addition salts thereof, wherein R_1' represents R_1 as defined herein above, or R_1' is a group convertible to R_1, with an activated derivative of a carboxylic acid of the formula



(III)

wherein R_2, R_3 and R_4 have meanings as defined herein, and R_5' represents R_5 as defined herein above, or R_5' is a group convertible to R_5, to afford a compound of the formula

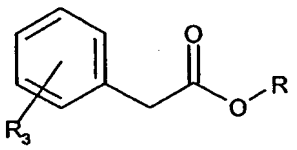


(I')

wherein R_1', R_2, R_3, R_4 and R_5' have meanings as defined for formulae (II) and (III).

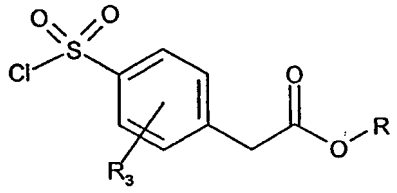
In the coupling reaction cited herein above, an activated derivative of a carboxylic acid, e.g., those corresponding to carboxylic acids of formula (III), include acid chlorides, bromides and fluorides, mixed anhydrides, lower alkyl esters and activated esters thereof, and adducts formed with coupling agents, such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI), 1-hydroxy benzotriazole (HOBt), O-(1,2-dihydro-2-oxo-1-pyridyl)-N,N,N',N'-tetramethyluronium tetrafluoroborate, benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBOP) and the like. Mixed anhydrides are preferably such from pivalic acid, or lower alkyl hemiesters of carbonic acids, such as ethyl or isobutyl analogs. Activated esters include, for example, succinimido, phthalimido or 4-nitrophenyl esters. The reaction of an activated derivative of a carboxylic acid, e.g., those corresponding to carboxylic acids of formula (III), with an amine, e.g., those of formula (II), may be carried out in the presence of a base, such as pyridine, triethylamine (TEA), diisopropylethylamine (DIEA) or N-methylmorpholine (NMM) in an inert organic solvent, such as dichloromethane (DCM), N,N-dimethylformamide (DMF) or tetrahydrofuran (THF), or a mixture of solvents thereof. Carboxylic acids of formula (III) may be converted to their activated derivatives using methods described herein or according to methods generally known in the art, e.g., a carboxylic acid of formula (III) may be treated with a chlorinating agent, such as thionyl chloride or oxalyl chloride, to afford a corresponding acid chloride thereof, or by the treatment of a coupling agent such as EDCI or HOBt, or a mixture of coupling agents thereof.

Amines of formula (II) and carboxylic acids of formula (III) are known, or if they are novel they may be prepared using methods described herein in the illustrative Examples, or modifications thereof, or using methods well known in the art. For example, compounds of formula (III) may be prepared by treating an ester of the formula



(IV)

wherein R_3 has a meaning as defined herein above, and R is lower alkyl, preferably, methyl or ethyl, with chlorosulfonic acid to afford a compound of the formula



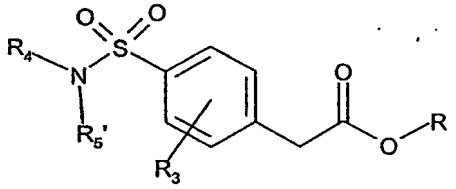
(V)

wherein R_3 and R have meanings as defined herein above, optionally in the presence of an intrinsic organic solvent. Preferably, the reaction is carried out without an intrinsic organic solvent.

A compound of formula (V) may then be treated with an amine of the formula

$$R_4\text{-NH-}R_5' \qquad \text{(VI)},$$

or an acid addition salt thereof, wherein R_4 and R_5' have meanings as defined herein above, in the presence of a base, such as pyridine, TEA, DIEA or NMM, in an inert organic solvent, such as DCM, DMF or THF, or a mixture of solvents thereof, to afford a compound of the formula



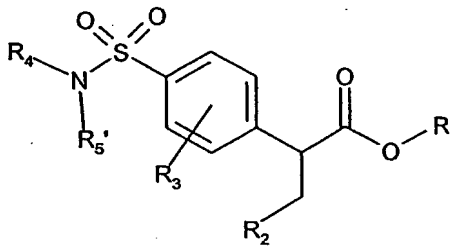
(VII)

wherein R_3, R_4, R_5' and R have meanings as defined herein above. Preferably, the reaction is conducted at a temperature ranging from about -4°C to room temperature (RT), more preferably, the reaction temperature is about 0°C.

A resulting compound of formula (VII) may then be treated with a base, such as sodium hydride, lithium diisopropylamide (LDA) or lithium bis(trimethylsilyl)amide (LHMDS), preferably LDA, followed by addition of an alkylating agent of the formula

$$R_2\text{-}(CH_2)\text{-Lg} \qquad \text{(VIII)}$$

wherein R_2 has a meaning as defined herein above, and Lg represents a leaving group, such as chloride, bromide, iodide, mesylate, tosylate or triflate, preferably iodide, to afford a compound of the formula



(IX)

wherein R_2, R_3, R_4, R_5' and R have meanings as defined herein above. The alkylation step is preferably conducted in a polar organic solvent, such as THF, DMF, N-methylpyrrolidone (NMP), 1,3-dimethyl-3,4,5,6-tetrahydro-2(*1H*)-pyridone (DMPU) or 1,3-dimethyl-3,4,5,6-tetrahydro-2(*1H*)-pyrimidinone (DMTP), or in a mixture of solvents thereof.

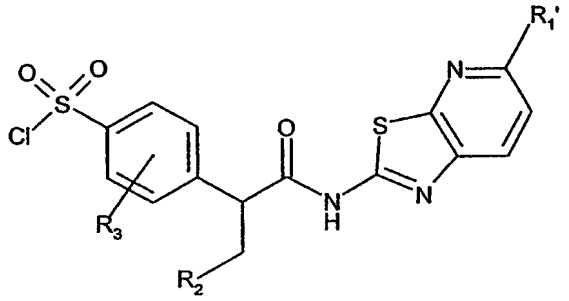
A resulting compound of formula (IX) may then be hydrolyzed, e.g., in the presence of an aqueous base such as sodium, lithium or potassium hydroxide and an organic solvent such as THF or lower alcohol, preferably, methanol or ethanol, to afford a carboxylic acid of formula (III) wherein R_2, R_3, R_4 and R_5' have meanings as defined herein above.

A carboxylic acid of formula (III) may then be coupled with an amine of formula (II) under reaction conditions as described herein above to afford a compound of formula (I') wherein R_1', R_2, R_3, R_4 and R_5' have meanings as defined herein above, e.g., via conversion of the acid to the corresponding acid chloride or in the presence of a coupling agent such as EDCI, HOBt or PyBOP, or a mixture of coupling agents thereof.

Alternatively, compounds of formula (I) may be prepared as outlined herein below.

Method B:

Compounds of formula (I) may be obtained by reacting a compound of the formula

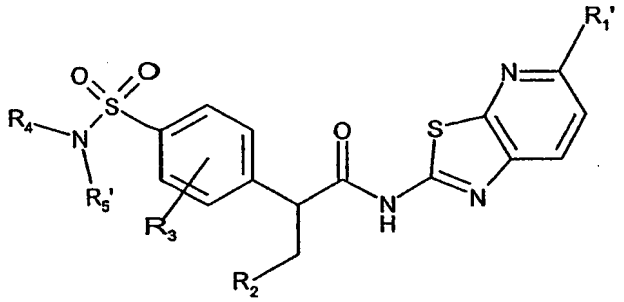


(X)

wherein R_2 and R_3 have meanings as defined herein above, and R_1' represents R_1 as defined herein above, or R_1' is a group convertible to R_1, with an amine of the formula

R_4-NH-R_5' (VI),

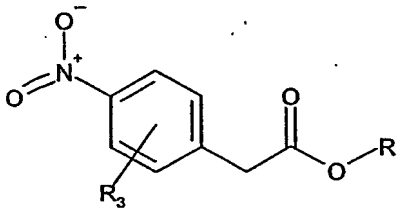
or an acid addition salt thereof, wherein R_4 has a meaning as defined herein, and R_5' represents R_5 as defined herein above, or R_5' is a group convertible to R_5, in the presence of a base, such as pyridine, TEA, DIEA or NMM, in an inert organic solvent, such as DCM, DMF or THF, or a mixture of solvents thereof, to afford a compound of the formula



(I')

wherein R_1', R_2, R_3, R_4 and R_5' have meanings as defined herein above.

Compounds of formula (X) may be prepared, e.g., by treating a compound of the formula

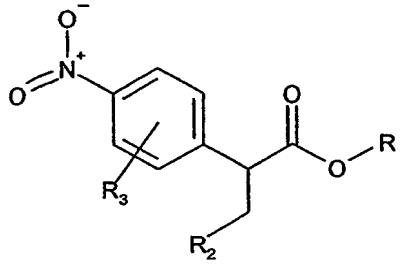


(XI)

wherein R_3 and R have meanings as defined herein above, with a base, such as sodium hydride, LDA or LHMDS, preferably LDA, followed by addition of an alkylating agent of the formula

R_2-(CH_2)-Lg (VIII)

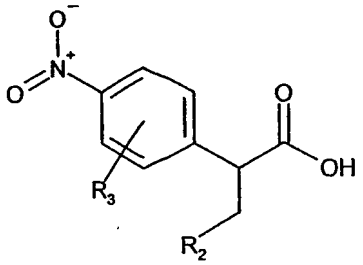
wherein R_2 has a meaning as defined herein above, and Lg represents a leaving group, such as chloride, bromide, iodide, mesylate, tosylate or triflate, preferably iodide, to afford a compound of the formula



(XII)

wherein R_2, R_3 and R have meanings as defined herein above. The alkylation step is preferably conducted in a polar organic solvent, such as THF, DMF, NMP, DMPU or DMTP, or in a mixture of solvents thereof.

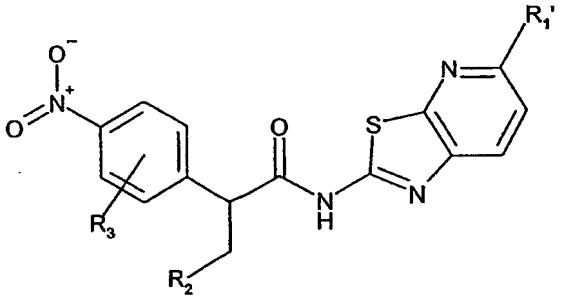
A resulting compound of formula (XII) may then be hydrolyzed, e.g., in the presence of an aqueous base, such as sodium, lithium or potassium hydroxide and an organic solvent such as THF or lower alcohol, preferably, methanol or ethanol, to afford a carboxylic acid of the formula



(XIII)

wherein R_2 and R_3 have meanings as defined herein above.

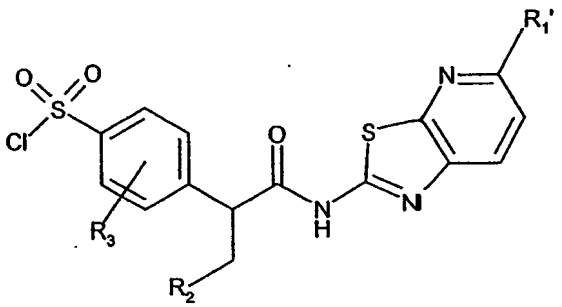
A carboxylic acid of formula (XIII) may then be coupled with an amine of formula (II) under reaction conditions as described herein above to afford a compound of the formula



(XIV)

wherein R_1', R_2 and R_3 have meanings as defined herein above, e.g., via conversion of the acid to the corresponding acid chloride or in the presence of a coupling agent, such as EDCI, HOBt or PyBOP, or a mixture of coupling agents thereof.

A resulting compound of formula (XIV) may then be converted to a sulfonyl chloride derivative of the formula



(XV)

wherein R_1', R_2 and R_3 have meanings as defined herein above, by reduction of the nitro group to the amino group, e.g., using iron powder in the presence of a mixture of acetic acid and a lower alcohol, such as ethanol, followed by diazotization reaction and subsequent treatment with, e.g., sulfur dioxide in the presence of copper(II) chloride and acetic acid.

Finally, a sulfonyl chloride derivative of formula (XV) may be treated with an amine of the formula

$$R_4\text{-NH-}R_5' \qquad \text{(VI)},$$

or an acid addition salt thereof, wherein R_4 and R_5' have meanings as defined herein above, in the presence of a base, such as pyridine, TEA, DIEA or NMM, in an inert organic solvent, such as DCM, DMF or THF, or a mixture of solvents thereof, to afford a compound of formula (I') wherein R_1', R_2, R_3, R_4 and R_5' have meanings as defined herein above.

The processes described herein above may be conducted under inert atmosphere, preferably under nitrogen atmosphere.

In starting compounds and intermediates which are converted to the compounds of the present invention in a manner described herein, functional groups present, such as amino, thiol, carboxyl and hydroxyl groups, are optionally protected by conventional protecting groups that are common in preparative organic chemistry. Protected amino, thiol, carboxyl and hydroxyl groups are those that can be converted under mild conditions into free amino thiol, carboxyl and hydroxyl groups without the molecular framework being destroyed or other undesired side reactions taking place.

The purpose of introducing protecting groups is to protect the functional groups from undesired reactions with reaction components under the conditions used for carrying out a desired chemical transformation. The need and choice of protecting groups for a particular reaction is known to those skilled in the art and depends on the nature of the functional

group to be protected (hydroxyl group, amino group, etc.), the structure and stability of the molecule of which the substituent is a part and the reaction conditions.

Well-known protecting groups that meet these conditions and their introduction and removal are described, e.g., in McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London, NY (1973); and Greene and Wuts, "Protective Groups in Organic Synthesis", John Wiley and Sons, Inc., NY (1999).

The above-mentioned reactions are carried out according to standard methods, in the presence or absence of diluent, preferably, such as are inert to the reagents and are solvents thereof, of catalysts, condensing or said other agents, respectively and/or inert atmospheres, at low temperatures, RT or elevated temperatures, preferably at or near the boiling point of the solvents used, and at atmospheric or super-atmospheric pressure. The preferred solvents, catalysts and reaction conditions are set forth in the appended illustrative Examples.

The invention further includes any variant of the present processes, in which an intermediate product obtainable at any stage thereof is used as starting material and the remaining steps are carried out, or in which the starting materials are formed *in situ* under the reaction conditions, or in which the reaction components are used in the form of their salts or optically pure antipodes.

Compounds of the invention and intermediates can also be converted into each other according to methods generally known *per se*.

The invention also relates to any novel starting materials, intermediates and processes for their manufacture.

Depending on the choice of starting materials and methods, the new compounds may be in the form of one of the possible isomers or mixtures thereof, for example, as substantially pure geometric (*cis* or *trans*) isomers, diastereomers, optical isomers (antipodes), racemates or mixtures thereof. The aforesaid possible isomers or mixtures thereof are within the purview of this invention.

Any resulting mixtures of isomers can be separated on the basis of the physicochemical differences of the constituents, into the pure geometric or optical isomers, diastereomers, racemates, for example, by chromatography and/or fractional crystallization.

Any resulting racemates of final products or intermediate, e.g., acids of formulae (III) and (XIII), can be resolved into the optical antipodes by known methods, e.g., by separation of the diastereomeric salts thereof, obtained with an optically active acid or base and liberating the optically active acidic or basic compound, e.g., acids of formulae (III) and (XIII) can be resolved using 1-phenylethylamine. Furthermore, the thiazolopyridine moiety may be employed to resolve the compounds of the present invention into their optical antipodes, e.g., by fractional crystallization of a salt formed with an optically active acid, e.g., tartaric acid, dibenzoyl tartaric acid, diacetyl tartaric acid, di-O,O'-*p*-toluoyl tartaric acid, mandelic acid, malic acid or camphor-10-sulfonic acid. Racemic products can also be resolved by chiral chromatography, e.g., high pressure liquid chromatography (HPLC) using a chiral adsorbent.

Finally, compounds of the invention are either obtained in the free form, or in a salt form thereof, preferably, in a pharmaceutically acceptable salt form thereof, or as a prodrug derivative thereof.

Compounds of the instant invention which contain acidic groups may be converted into salts with pharmaceutically acceptable bases. Such salts include alkali metal salts, like sodium, lithium and potassium salts; alkaline earth metal salts, like calcium and magnesium salts; ammonium salts with organic bases, e.g., trimethylamine salts, diethylamine salts, tris(hydroxymethyl)methylamine salts, dicyclohexylamine salts and N-methyl-D-glucamine salts; salts with amino acids like arginine, lysine and the like. Salts may be formed using conventional methods, advantageously in the presence of an ethereal or alcoholic solvent, such as a lower alkanol. From the solutions of the latter, the salts may be precipitated with ethers, e.g., diethyl ether. Resulting salts may be converted into the free compounds by treatment with acids. These or other salts can also be used for purification of the compounds obtained.

Compounds of the invention, in general, may be converted into acid addition salts, especially pharmaceutically acceptable salts. These are formed, e.g., with inorganic acids, such as mineral acids, e.g., sulfuric acid, phosphoric or hydrohalic acid, or with organic carboxylic acids, such as (C_1-C_4)-alkanecarboxylic acids which, e.g., are unsubstituted or substituted by halogen, e.g., acetic acid, such as saturated or unsaturated dicarboxylic acids, e.g., oxalic, succinic, maleic or fumaric acid, such as hydroxycarboxylic acids, e.g., glycolic, lactic, malic, tartaric or citric acid, such as amino acids, e.g., aspartic or glutamic acid, or with organic

sulfonic acids, such as (C_1-C_4)-alkylsulfonic acids, e.g., methanesulfonic acid; or arylsulfonic acids which are unsubstituted or substituted (for example by halogen). Preferred are salts formed with hydrochloric acid, maleic acid and methanesulfonic acid.

Prodrug derivatives of any compound of the invention are derivatives of said compounds which following administration release the parent compound *in vivo* via some chemical or physiological process, e.g., a prodrug on being brought to the physiological pH or through enzyme action is converted to the parent compound. Exemplary prodrug derivatives are, e.g., esters of free carboxylic acids and *S*-acyl and *O*-acyl derivatives of thiols, alcohols or phenols, wherein acyl has a meaning as defined herein. Preferred are pharmaceutically acceptable ester derivatives convertible by solvolysis under physiological conditions to the parent carboxylic acid, e.g., lower alkyl esters, cycloalkyl esters, lower alkenyl esters, benzyl esters, mono- or di-substituted lower alkyl esters, such as the ω-(amino, mono- or di-lower alkylamino, carboxy, lower alkoxycarbonyl)-lower alkyl esters, the α-(lower alkanoyloxy, lower alkoxycarbonyl or di-lower alkylaminocarbonyl)-lower alkyl esters, such as the pivaloyloxymethyl ester and the like conventionally used in the art.

In view of the close relationship between the free compounds, the prodrug derivatives and the compounds in the form of their salts, whenever a compound is referred to in this context, a prodrug derivative and a corresponding salt is also intended, provided such is possible or appropriate under the circumstances.

The compounds, including their salts, can also be obtained in the form of their hydrates, or include other solvents used for their crystallization.

As described herein above, the compounds of the present invention may be employed for the treatment of conditions mediated by glucokinase activity. Such compounds may thus be employed therapeutically for the treatment of impaired glucose tolerance, Type 2 diabetes and obesity.

The present invention further provides pharmaceutical compositions comprising a therapeutically effective amount of a pharmacologically active compound of the instant invention, alone or in combination with one or more pharmaceutically acceptable carriers.

The pharmaceutical compositions according to the invention are those suitable for enteral, such as oral or rectal; transdermal and parenteral administration to mammals, including

man, for the treatment of conditions mediated by glucokinase activity. Such conditions include impaired glucose tolerance, Type 2 diabetes and obesity.

Thus, the pharmacologically active compounds of the invention may be employed in the manufacture of pharmaceutical compositions comprising an effective amount thereof in conjunction or admixture with excipients or carriers suitable for either enteral or parenteral application. Preferred are tablets and gelatin capsules comprising the active ingredient together with:

a) diluents, e.g., lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine;

b) lubricants, e.g., silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol; for tablets also

c) binders, e.g., magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and or polyvinylpyrrolidone; if desired

d) disintegrants, e.g., starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and/or

e) absorbants, colorants, flavors and sweeteners.

Injectable compositions are preferably aqueous isotonic solutions or suspensions, and suppositories are advantageously prepared from fatty emulsions or suspensions.

Said compositions may be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In addition, they may also contain other therapeutically valuable substances. Said compositions are prepared according to conventional mixing, granulating or coating methods, respectively, and contain about 0.1-75%, preferably about 1-50%, of the active ingredient.

Suitable formulations for transdermal application include a therapeutically effective amount of a compound of the invention with carrier. Advantageous carriers include absorbable pharmacologically acceptable solvents to assist passage through the skin of the host. Characteristically, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound of the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin.

Accordingly, the present invention provides pharmaceutical compositions as described above for the treatment of conditions mediated by glucokinase activity, preferably, impaired glucose tolerance, Type 2 diabetes and obesity.

The pharmaceutical compositions may contain a therapeutically effective amount of a compound of the invention as defined above, either alone or in a combination with another therapeutic agent, e.g., each at an effective therapeutic dose as reported in the art. Such therapeutic agents include:

a) antidiabetic agents, such as insulin, insulin derivatives and mimetics; insulin secretagogues such as the sulfonylureas, e.g., Glipizide, glyburide and Amaryl; insulinotropic sulfonylurea receptor ligands such as meglitinides, e.g., nateglinide and repaglinide; protein tyrosine phosphatase-1B (PTP-1B) inhibitors such as PTP-112; GSK3 (glycogen synthase kinase-3) inhibitors such as SB-517955, SB-4195052, SB-216763, NN-57-05441 and NN-57-05445; RXR ligands such as GW-0791 and AGN-194204; sodium-dependent glucose cotransporter inhibitors such as T-1095; glycogen phosphorylase A inhibitors such as BAY R3401; biguanides such as metformin; alpha-glucosidase inhibitors such as acarbose; GLP-1 (glucagon like peptide-1), GLP-1 analogs such as Exendin-4 and GLP-1 mimetics; and DPPIV (dipeptidyl peptidase IV) inhibitors such as LAF237;

b) hypolipidemic agents such as 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors, e.g., lovastatin, pitavastatin, simvastatin, pravastatin, cerivastatin, mevastatin, velostatin, fluvastatin, dalvastatin, atorvastatin, rosuvastatin and rivastatin; squalene synthase inhibitors; FXR (farnesoid X receptor) and LXR (liver X receptor) ligands; cholestyramine; fibrates; nicotinic acid and aspirin;

c) anti-obesity agents such as orlistat; and

d) anti-hypertensive agents, e.g., loop diuretics such as ethacrynic acid, furosemide and torsemide; angiotensin converting enzyme (ACE) inhibitors such as benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perinodopril, quinapril, ramipril and trandolapril; inhibitors of the Na-K-ATPase membrane pump such as digoxin; neutralendopeptidase (NEP) inhibitors; ACE/NEP inhibitors such as omapatrilat, sampatrilat and fasidotril; angiotensin II antagonists such as candesartan, eprosartan, irbesartan, losartan, telmisartan and valsartan, in particular valsartan; renin inhibitors such as ditekiren, zankiren, terlakiren, aliskiren, RO 66-1132 and RO-66-1168; β-adrenergic receptor blockers such as acebutolol, atenolol, betaxolol, bisoprolol, metoprolol, nadolol, propranolol, sotalol and timolol; inotropic agents such as digoxin, dobutamine and milrinone; calcium channel blockers such as

amlodipine, bepridil, diltiazem, felodipine, nicardipine, nimodipine, nifedipine, nisoldipine and verapamil; aldosterone receptor antagonists; and aldosterone synthase inhibitors.

Other specific anti-diabetic compounds are described by Patel Mona in *Expert Opin Investig Drugs*, 2003, 12(4), 623-633, in the figures 1 to 7, which are herein incorporated by reference. A compound of the present invention may be administered either simultaneously, before or after the other active ingredient, either separately by the same or different route of administration or together in the same pharmaceutical formulation.

The structure of the therapeutic agents identified by code numbers, generic or trade names may be taken from the actual edition of the standard compendium "The Merck Index" or from databases, e.g., Patents International (e.g. IMS World Publications). The corresponding content thereof is hereby incorporated by reference.

Accordingly, the present invention provides pharmaceutical compositions comprising a therapeutically effective amount of a compound of the invention in combination with a therapeutically effective amount of another therapeutic agent, preferably selected from anti-diabetics, hypolipidemic agents, anti-obesity agents or anti–hypertensive agents, most preferably from antidiabetics or hypolipidemic agents as described above.

The present invention further relates to pharmaceutical compositions as described above for use as a medicament.

The present invention further relates to use of pharmaceutical compositions or combinations as described above for the preparation of a medicament for the treatment of conditions mediated by glucokinase activity, preferably, impaired glucose tolerance, Type 2 diabetes and obesity.

Thus, the present invention also relates to a compound of formula (I) for use as a medicament; to the use of a compound of formula (I) for the preparation of a pharmaceutical composition for the prevention and/or treatment of conditions mediated by glucokinase activity, and to a pharmaceutical composition for use in conditions mediated by glucokinase activity comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable diluent or carrier therefore.

The present invention further provides a method for the prevention and/or treatment of conditions mediated by glucokinase activity, which comprises administering a therapeutically effective amount of a compound of the present invention.

A unit dosage for a mammal of about 50-70 kg may contain between about 1 mg and 1000 mg, advantageously between about 5-500 mg of the active ingredient. The therapeutically effective dosage of active compound is dependent on the species of warm-blooded animal (mammal), the body weight, age and individual condition, on the form of administration, and on the compound involved.

In accordance with the foregoing the present invention also provides a therapeutic combination, e.g., a kit, kit of parts, e.g., for use in any method as defined herein, comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, to be used concomitantly or in sequence with at least one pharmaceutical composition comprising at least another therapeutic agent, preferably selected from anti-diabetic agents, hypolipidemic agents, anti-obesity agents and anti-hypertensive agents, or a pharmaceutically acceptable salt thereof. The kit may comprise instructions for its administration.

Similarly, the present invention provides a kit of parts comprising: (i) a pharmaceutical composition of the invention; and (ii) a pharmaceutical composition comprising a compound selected from an anti-diabetic, a hypolipidemic agent, an anti-obesity agent and an anti-hypertensive agent, or a pharmaceutically acceptable salt thereof, in the form of two separate units of the components (i) to (ii).

Likewise, the present invention provides a method as defined above comprising co-administration, e.g., concomitantly or in sequence, of a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a second drug substance, said second drug substance being an anti-diabetic, a hypolipidemic agent, an anti-obesity agent or an anti-hypertensive agent, e.g., as indicated above.

Preferably, a compound of the invention is administered to a mammal in need thereof.

Preferably, a compound of the invention is used for the treatment of a disease which responds to modulation of the glucokinase activity.

Preferably, the condition associated with glucokinase activity is selected from impaired glucose tolerance, Type 2 diabetes and obesity.

Finally, the present invention provides a method or use which comprises administering a compound of formula (I) in combination with a therapeutically effective amount of an anti-diabetic agent, a hypolipidemic agent, an anti-obesity agent or an anti-hypertensive agent.

Ultimately, the present invention provides a method or use which comprises administering a compound of formula (I) in the form of a pharmaceutical composition as described herein.

As used throughout the specification and in the claims, the term "treatment" embraces all the different forms or modes of treatment as known to those of the pertinent art and in particular includes preventive, curative, delay of progression and palliative treatment.

The above-cited properties are demonstrable *in vitro* and *in vivo* tests using advantageously mammals, e.g., mice, rats, dogs, monkeys or isolated organs, tissues and preparations thereof. Said compounds can be applied *in vitro* in the form of solutions, e.g., preferably aqueous solutions, and *in vivo* either enterally, parenterally, advantageously intravenously, e.g., as a suspension or in aqueous solution. The dosage *in vitro* may range between about 10^{-2} molar and 10^{-9} molar concentrations. A therapeutically effective amount *in vivo* may range depending on the route of administration, between about 0.1 mg/kg and 1000 mg/kg, preferably between about 1 mg/kg and 100 mg/kg.

The activity of compounds according to the invention may be assessed by the following methods or methods well-described in the art:

The glucokinase activation *in vitro* may be determined by measuring the activation of recombinant GST-GK by a compound of the present invention in the absence or the presence of GKRP, a 68,000 Da protein inhibitor of GK. In these assays, formation of glucose-6-phosphate is coupled directly to the formation of thioNADH. GST-GK catalyzes the reaction of glucose and Mg-ATP to produce glucose-6-phosphate and ADP. Glucose-6-phosphate dehydrogenase (G6PDH) reduces thionicotinamide (thioNAD) to thioNADH. The assay measures the formation of NADH at 405 nM.

The basic GK assay components are as follows: 25 mM HEPES (pH 7.1), 25 mM KCl, 2.5 mM $MgCl_2$, 1 mM ATP (Sigma A-5394), 1 mM DTT, 1 mM thioNAD (Sigma T-7375), 80 units/mL G6PDH (Sigma G-5885), 10 mM glucose and 8.7 mg/mL GST-GK (110 nM). For assessing reversal of GK inhibition by GKRP, 20 µM Fructose-1-phosphate (F-6-P) and 25 µg/mL of recombinant GKRP (370 nM) are added to these assay components. F-1-P at

1 µM is used as a control in the GK/GKRP assay. F-1-P reverses inhibition of GST–GK by GKRP.

The assay is done in standard, 96-well, round-bottom plates and the total assay volume is 25 µL. Compounds are serially diluted into 100% DMSO and 0.5 µL of diluted compound in 100% DMSO is added to the assay plate. Assay reagents (24.5 µL) are added using a Zymark robotic platform. Buffer, containing HEPES, $MgCl_2$, KCl, thioNAD, G6PDH, F-6-P, glucose, GKRP and GST-GK, are added (5 µL) using the Zymark 8-channel hand pipet. The reaction is then initiated by adding 19.5 µL of buffer containing HEPES, $MgCl_2$, KCl, DTT and ATP using the Zymark Reagent Addition Station/Reagent Addition Module. The plates are then delivered via the Zymark XP arm to a Thermomax plate reader and read kinetically over three min at 405 nM at RT. Units are expressed as milli-optical density per minute (mOD/min).

The glucokinase activation in rat hepatocytes may be determined as follows:

Hepatocytes are isolated by collagenase perfusion of the livers of overnight-fasted male Harlen Sprague-Dawley rats (Charles River Laboratories, Raleigh, NC) as previously described (see Berry et al., *J. Cell Biol.*, Vol. 43, pp. 506-520 (1969)). The cells are washed three times each with 100 mL of glucose-free Dulbecco's Modified Eagle medium (DMEM, Gibco BRL) containing 5% fetal bovine serum (FBS) and then suspended in glucose-free DMEM/5% FBS. Cells are plated in collagen coated 24-well plates (Becton Dickinson) at a density of 3×10^5 cells/well in 1 mL of William's Medium E (Sigma) supplemented with 5% FBS, and incubated at 37°C in 5% CO_2/95% air. After cell attachment (~4 h), the medium is replaced with serum-free DMEM containing 5 mM glucose and 10 nM dexamethasone (Sigma), and cells are cultured further for 16-20 h prior to use.

The rate of glucose phosphorylation is determined by the release of ^3H_2O from [2-^{3}H]glucose. The medium from the cultured hepatocytes is removed, and the cells are pre-incubated in 150 µL of fresh serum-free DMEM containing 5 mM glucose and compound (1, 10 and 30 µM) or DMSO for 3 h at 37°C. The final concentration of DMSO is 0.2%. The medium is then removed and 150 µL of a fresh mixture of DMEM/5 mM glucose containing compound or DMSO, and 1 µCi of [2-^{3}H]glucose (NEN) is added. As a positive control for stimulation of glucose phosphorylation, cells are pre-incubated in serum-free DMEM/5 mM glucose medium containing DMSO for 3 h and then are incubated for 1 h in labeled glucose medium containing 0.5 mM fructose/DMSO (precursor of F-1-P, AnalaR® from BDH). All

conditions are tested in quadruplicate where one well per plate received 200 µL of the appropriate medium plus labeled glucose (instead of 150 µL) of which 50 µL is immediately removed and placed in a 1.2 mL microfuge tube (Costar) containing 10 µL of 1 N HCl. This sample is used as a 0-minute time point for determining background ^3H_2O release (exchange values). Following the addition of the labeled glucose media, hepatocytes are incubated at 37°C on a slow moving rocker for 1 h.

On termination of the incubation, 50 µL of the culture medium is collected into microfuge tubes containing 10 µL of 1 N HCl, and determination of ^3H_2O. The tubes are left uncapped and each is placed inside a 20 mL glass scintillation vial (Wheaton) containing 1.5 mL of deionized water. The vials are capped tightly and incubated at 37°C in a dry incubator for 2 days ($^3H_20$ from the reaction mixture will equilibrate with the water in the vial). A standard curve is generated using [^{3}H]H_2O (NEN) to correct for exchange. 50 µL aliquots of serial dilutions of the labeled water are added to 10 µL of 1 N HCl and exchange is performed as described for the samples (typically, approximately 90% exchange is observed). The microfuge tubes are then removed from the vials carefully to minimize the removal of any water from the vial and 18 mL of scintillation cocktail (Ready Safe, Beckman Coulter) is then added to each vial. The ^{3}H-label recovered from [2-^{3}H]glucose in the water is determined using a Beckman Model LS500 scintillation counter and the counts (minus the 0-time point) are corrected for recovery of ^3H_2O. The amount of glucose de-tritiated in nanomoles/h per 10^6 cells is calculated, and the results are expressed as percent increase over the DMSO control.

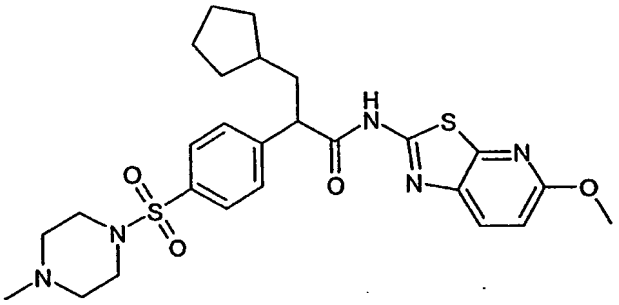
Illustrative of the invention, the compound of Example 1 demonstrates an EC_{50} of about 251 nM in the *in vitro* assay measuring the activation of recombinant GST-GK.

The following Examples are intended to illustrate the invention and are not to be construed as being limitations thereon. If not mentioned otherwise, all evaporations are performed under reduced pressure, preferably between about 50 mmHg and 100 mmHg. The structure of final products, intermediates and starting materials is confirmed by standard analytical methods, e.g., microanalysis, melting point (m.p.) and spectroscopic characteristics, e.g., MS, IR and NMR. Abbreviations used are those conventional in the art.

The following compounds may be prepared according to Method A.

Example 1

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide



A. Phenylacetic acid ethyl ester

A solution of phenylacetic acid (50 g, 0.36 mol) in ethanol (150 mL) is treated with catalytic amount of sulfuric acid (4 mL). The reaction mixture is refluxed for 4 h . The reaction is then concentrated in vacuo. The residue is dissolved in diethyl ether (300 mL) and washed with saturated aqueous sodium bicarbonate solution (2 x 50 mL) and water (1 x 100 mL). The organic layer dried over sodium sulfate filtered and concentrated in vacuo to give phenylacetic acid ethyl ester as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.2 (t, J=7.2, 3H), 3.6 (s, 2H), 4.1 (q, J=7.2, 2H), 7.3 (m, 5H); MS 165 $[M+1]^+$.

B. (4-Chlorosulfonyl-phenyl)-acetic acid ethyl ester

To a cooled chlorosulfonic acid (83.83 g, 48 mL, 0.71 mol) under nitrogen is added the title A compound, phenylacetic acid ethyl ester (59 g, 0.35 mol) over a period of 1 h. Reaction temperature is brought to RT (28°C), then heated to 70°C, maintaining it at this temperature for 1 h while stirring. Reaction is cooled to RT and poured over saturated aqueous sodium chloride solution (200 mL) followed by extraction with DCM (2 x 200 mL). The organic layer is washed with water (5 x 100 mL), followed by saturated aqueous sodium chloride solution (1 x 150 mL). The organic layer dried over sodium sulfate, filtered and concentrated in vacuo to give crude (4-chlorosulfonyl-phenyl)acetic acid ethyl ester. Further column chromatography over silica gel (60 – 120 mesh), using 100% hexane afforded pure (4-chlorosulfonyl-phenyl)-acetic acid ethyl ester as a colorless oil.

C. [4-(4-Methyl-piperazine-1-sulfonyl)-phenyl]-acetic acid ethyl ester

A solution of N-methylpiperazine (9.23 g, 10.21 ml, 0.092 mol), DIEA (13 g, 17.4 mL, 0.10 mol) and DCM 80 mL is cooled to 0°C, and to this is added a solution of the title B

compound, (4-chlorosulfonyl-phenyl)-acetic acid ethyl ester (22 g, 0.083 mol) in 50 mL of DCM within 30 min. Reaction mixture stirred at 0°C for 2 h, and the reaction mixture is washed with water (100 mL), followed by 0.1 N aqueous hydrochloric acid solution (1 x 200 mL). The organic layer dried over sodium sulfate, filtered and concentrated under vacuo to give crude [4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-acetic acid ethyl ester. Column chromatography over silicagel (60 – 120 mesh), using ethyl acetate afforded pure [4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-acetic acid ethyl ester as white crystalline solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.3 (t, J=7.4, 3H), 2.3 (s, 3H), 2.5 (m, 4H), 3.0 (br s, 4H), 3.7 (s, 2H), 4.2 (q, J=7.4, 2H), 7.4 (d, J=8.3, 2H), 7.7 (d, J=7.3, 2H); MS 327 $[M+1]^+$.

D. 3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionic acid ethyl ester

A solution of the title C compound, [4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-acetic acid ethyl ester (15 g, 0.046 mol) in a mixture of THF (60 mL) and DMTP (10 mL) is cooled to –78°C under nitrogen. The resulting solution is stirred at –78°C for 45 min and to this is added LDA (25.6 mL, 6.40 g, 0.059 mol, 25% solution in THF / Hexane). A solution of iodomethylcyclopentane (11.60 g, 0.055 mol) in a mixture of DMTP (12 mL) and THF (20 mL) is added over a period of 15 min at –78°C and reaction mixture stirred at –78°C for 3 h further, followed by stirring at 25°C for 12 h. The reaction mixture is then quenched by the dropwise addition of saturated aqueous ammonium chloride solution (50 mL) and is concentrated in vacuo. The residue is diluted with water (50 mL) and extracted with ethyl acetate (3 x 100 mL). The organic solution is washed with a saturated aqueous sodium chloride (2 x 150 mL), dried over sodium sulfate, filtered and concentrated in vacuo. Column chromatography over silica gel (60 – 120 mesh), using 50% ethyl acetate in hexane as an eluent to afford 3-cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionic acid ethyl ester as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.9-2.1 (m, 11H), 1.2 (t, J=7.1, 3H), 2.3 (s, 3H), 2.5 (br s, 4H), 3.0 (br s, 4H), 3.6 (m, 1H), 4.1 (q, J=7.1, 2H), 7.5 (d, J=8.3, 2H), 7.7 (d, J=8.3, 2H); MS 409 $[M+1]^+$.

E. 3-Cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionic acid

A solution of the title D compound, 3-cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionic acid ethyl ester (14 g, 0.034 mol) in methanol:water (30 mL:10 mL) and sodium hydroxide (4.11 g, 0.10 mol) is stirred at 60°C for 8 h in an oil bath. The methanol is then removed in vacuo at 45-50°C. The residue is diluted with water (25 mL) and extracted with ether (1 x 40 mL). The aqueous layer is acidified to pH 5 with 3 N aqueous hydrochloric

acid solution. The precipitated solid is collected by vacuum filtration, washed with water (20 mL), followed by isopropyl alcohol (20 mL). Finally, solid cake is washed with 100 mL of hexane and dried under vacuum at 40°C for 6 h to give 3-cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionic acid as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.1-2.0 (m, 11H), 2.4 (s, 3H), 2.7 (br s, 4H), 3.1 (br s, 4H), 3.6 (m, 1H), 7.5 (d, J=8.3, 2H), 7.6 (d, J=8.3, 2H); MS 381 $[M+1]^+$.

F. 5-Methoxy-thiazolo[5,4-b]pyridin-2-ylamine

A solution of 6-methoxy-pyridin-3-ylamine (5.0 g, 0.0403 mol) in 10 mL of acetic acid is added slowly to a solution of potassium thiocyanate (20 g, 0.205 mol) in 100 mL of acetic acid at 0°C followed by a solution of bromine (2.5 mL, 0.0488 mol) in 5 mL of acetic acid. The reaction is stirred for 2 h at 0°C and then allowed to warm to RT. The resulting solid is collected by filtration and washed with acetic acid, then partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The insoluble material is removed by filtration and the organic layer is evaporated and dried to afford 5-methoxy-thiazolo[5,4-b]pyridin-2-ylamine as a tan solid.

G. 3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide

A solution of the title E compound, 3-cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionic acid (5 g, 0.013 mol) in DCM (250 mL) is cooled to 0°C and then charged HOBt hydrate (2.66 g, 0.019 mol), followed by EDCI hydrochloride (6 g, 0.031 mol). The reaction mixture is stirred at 0°C for 5 h. After that the solution of the title F compound, 5-methoxy-thiazolo[5,4-b]pyridin-2-ylamine (2.36 g, 0.013 mol) and DIEA (8 mL, 0.046 mol) in a mixture of DCM (60 mL) and DMF (20 mL) is added dropwise over 30 min. Reaction temperature is maintained at 0°C for 3 h, then at RT (28°C) for 3 days. Reaction is diluted with (60 mL) of water and the organic layer is separated and washed with saturated sodium bicarbonate solution (2 x 50 mL) followed by water washing (2 x 50 mL) and saturated sodium chloride aqueous solution (1 x 150 mL). Finally the organic layer is dried over sodium sulfate, filtered, and evaporated under vacuo. The crude product is purified using column chromatography over silica gel (60-120 mesh), using 40% ethyl acetate in hexane as an eluent to afford 3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.9-2.1 (m, 11H), 2.2 (s, 3H), 2.5 (br s, 4H), 3.1 (br s, 4H), 3.7 (m, 1H), 4.0 (s, 3H), 6.8 (d,

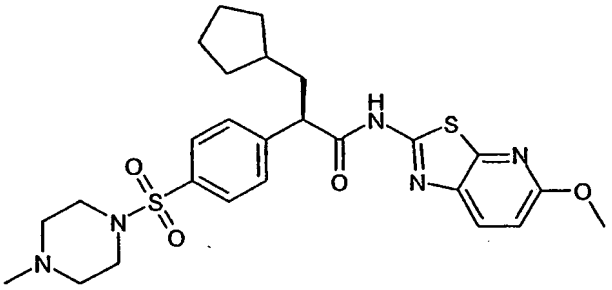
J=8.8, 1H), 7.5 (d, J=8.3, 2H), 7.7 (d, J=8.3, 2H), 7.8 (d, J=8.8, 1H), 8.6 (s, 1H); MS 617 $[M+1]^+$.

H. 3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide dihydrochloride

The title G compound, 3-cyclopentyl-2-(4-methyl piperazinyl sulfonyl)phenyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)propionamide (2.8 g, 0.0051 mol) is added to a cooled solution of 10% hydrochloric acid in isopropanol (3.75 mL). The reaction mixture is stirred at 0°C for 1 h and then at RT for 2 h. The solid is separated, triturated with 10 mL of isopropanol and collected by vacuum filtration and washed with 50 mL of hexane. The solid is dried at 70°C for 48 h to afford 3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide dihydrochloride as an off white solid.

Example 2

(*R*)-3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide



The title compound is obtained analogously to Example 1 by employing the following additional resolution step:

The racemic title E compound of Example 1, 3-cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionic acid (10 g, 0.026 mol) in 1,4-dioxane (500 mL) is treated in a three necked 1 liter flask, equipped with heating mantle, water condenser, calcium chloride guard tube and mechanical stirrer with 3.18 g (0.026 mol) of (*R*)-(+)-1-phenylethylamine. This reaction mixture is then refluxed at 100°C for 1 h. The clear reaction solution is cooled to RT (27°C) and stirred for 10 h. The crystallized salt is collected by filtration under vacuum, washed with 5 mL of hexane and dried under vacuum to afford salt A.

The salt A is dissolved in 1,4-dioxane (500 mL) and heated at 100°C for 1 h. The clear reaction solution is cooled to RT (27°C) and stirred for 10 h. The crystallized product is

collected by filtration under vacuum, washed with 50 mL of hexane, and dried under vacuum to afford salt B.

The salt B is dissolved in 1,4-dioxane (290 mL) and heated at 100°C for 1 h. The clear reaction solution is cooled to RT (27°C) and stirred for 10 h. The crystallized product is collected by filtration under vacuum, washed with 30 mL of hexane, and dried under vacuum to afford salt C.

The salt C is dissolved in 1,4-dioxane (100 mL) and heated at 100°C for 1 h. The clear reaction solution is cooled to RT (27°C) and stirred for 10 h. The crystallized product is collected by filtration under vacuum, washed with 30ml of hexane, and dried under vacuum to afford salt D.

The salt D is treated with aqueous hydrochloric acid solution (20 mL, 1 mL of concentrated hydrochloric acid diluted with 100 mL of water) and stirred for 5 min. The white solid precipitates out and is collected by vacuum filtration, washed with 10 mL of cold water, 5 mL of isopropanol and 20 mL of hexane, and dried under vacuum to yield the hydrochloride salt of (*R*)-(-)-3-cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionic acid, salt E.

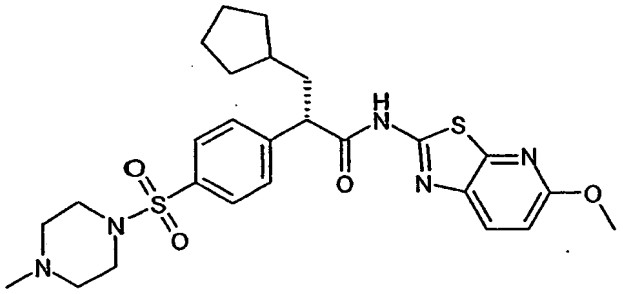
The salt E is neutralized by stirring with aqueous sodium bicarbonate solution (10 mL, 1 g of sodium bicarbonate dissolved in 120 mL of water) for 5 min. The precipitated solid is collected by filtration, washed with 10 mL of cold water, 100 mL of hexane, and dried to afford (*R*)-(-)-3-cyclopentyl-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionic acid: m.p. 202.2-203.4°C.

Alternatively, the title compound may be obtained by the resolution of the racemic title compound of Example 1 using the following preparative chiral HPLC method:

Column: Chiralcel OD-R (250 x 20 mm) Diacel make, Japan;
Solvent A: water:methanol:acetonitrile (10:80:10 v/v/v);
Solvent B: water:methanol:acetonitrile (05:90:05 v/v/v);
Using gradient elution: gradient program (time, min / %B): 0/0, 20/0, 50/100, 55/0, 70/0;
Flow rate: 6.0 mL/min; and
Detection: by UV at 305 nm.

Example 3

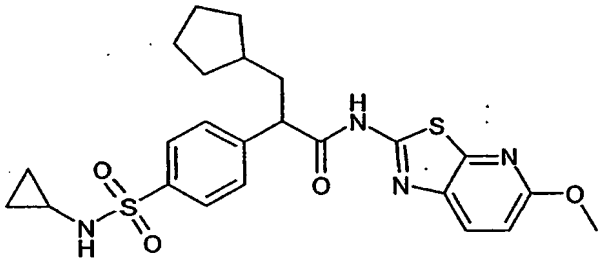
(*S*)-3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide



The title compound is prepared analogously to Example 2.

Example 4

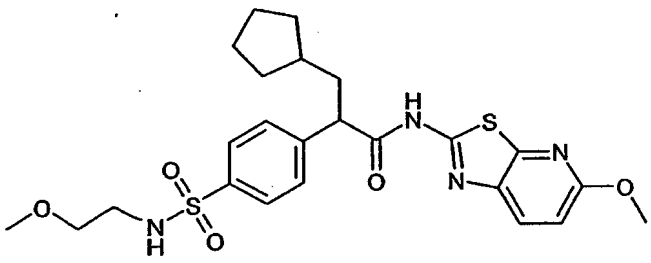
3-Cyclopentyl-2-(4-cyclopropylsulfamoyl-phenyl)-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide



The title compound is prepared analogously to Example 1: MS e/z (ES) 499 ($M-1^-$, 100%); m.p. 235-237°C; ^{1}H NMR ($CDCl_3$) δ 12.68 (s, 1H), 8.03 (d, J=8.8, 1H), 7.89 (d, J=2.4, 1H), 7.80 (d, J=8.4, 2H), 7.63 (d, J=8.4,2H), 6.91(d, J=8.8, 1H), 4.08 (t, J=7.2, 1H), 3.91 (s, 3H), 2.14-2.19 (m, 1H), 2.05-2.08 (m, 1H), 1.71-1.85 (m, 3H), 1.56-1.62 (m, 3 H), 1.42-1.45 (m, 2H), 1.09-1.16 (m, 2H), 0.44-0.48 (m, 2H), 0.34-0.38 (m, 2H).

Example 5

3-Cyclopentyl-2-[4-(2-methoxy-ethylsulfamoyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide

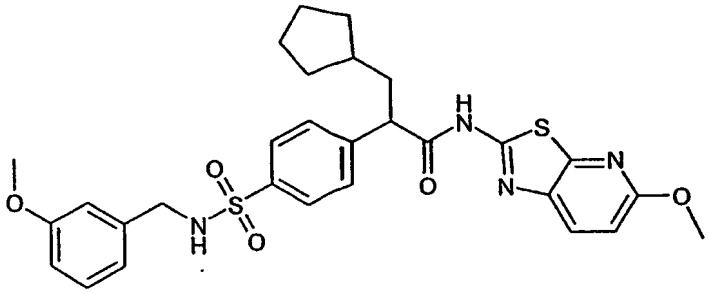


The title compound is prepared analogously to Example 1: MS e/z (ES) 519 ($M+1^+$, 100%); m.p. 209-211°C; ^{1}H NMR ($CDCl_3$) δ 12.66 (s, 1H), 8.03 (d, J=8.8, 1H), 7.78 (d, J=8.4, 2H),

7.69 (t, J=5.6, 1H),7.61 (d, J=8.4, 2H), 6.90 (d, J=8.8, 1H), 4.06 (t, J=7.6, 1H), 3.91 (s, 3H), 3.24-3.27 (m, 2H), 3.09 (s, 3H), 2.87-2.91 (m, 2H), 2.10-2.18 (m, 1H), 1.78-1.85 (m, 1H), 1.65-1.75 (m, 2H), 1.56-1.61 (m, 3H), 1.42-1.45 (m, 2H), 1.09-1.18 (m, 2H).

Example 6

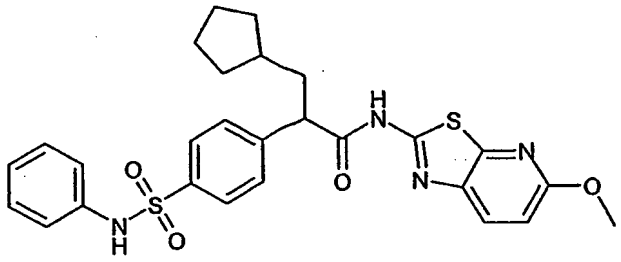
3-Cyclopentyl-2-[4-(3-methoxy-benzylsulfamoyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide



The title compound is prepared analogously to Example 1: MS e/z (ES) 579 (M-1$^-$, 100%); m.p. 179-181°C; ^{1}H NMR ($CDCl_3$) δ 12.67 (s, 1H), 8.15 (t, J=6.4, 1H), 8.04 (d, J=8.8, 1H), 7.72 (d, J=8.0, 2H), 7.55 (d, J=8.4, 2 H), 7.08 (t, J=8.0, 1H), 6.91 (d, J=8.8,1H), 6.70-6.75 (m, 2H), 6.63-6.68 (m, 1H), 4.04 (t, J=7.6, 1H), 3.98 (d, J=6.0, 2H), 3.91 (s, 3H), 3.63 (s, 3H), 2.10-2.19 (m, 1H), 1.70-1.88 (m, 3H), 1.50-1.60 (m, 3H), 1.40-1.48 (m, 2H), 1.10-1.22 (m, 2H).

Example 7

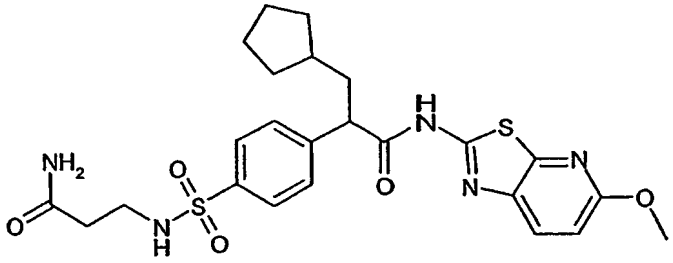
3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-(4-phenylsulfamoyl-phenyl)-propionamide



The title compound is prepared analogously to Example 1: MS e/z (ES) 535 (M-1$^-$, 100%); m.p. 223-226°C; ^{1}H NMR ($CDCl_3$) δ 12.65 (s, 1H), 10.30 (s, 1H), 8.02 (d, J=8.8, 1H), 7.75 (d, J=8.4, 2H), 7.56 (d, J=8.4, 2 H), 7.15-7.24 (m, 2H), 7.05-7.09 (m, 2H), 6.95-7.04 (m, 1H), 6.90 (d, J=8.8, 1H), 4.06 (t, J=7.6, 1H), 3.90 (s, 3H), 2.07-2.15 (m, 1H), 1.65-1.76 (m, 3H), 1.50-1.58 (m, 3H), 1.40-1.48 (m, 2H), 1.10-1.22 (m, 2H).

Example 8

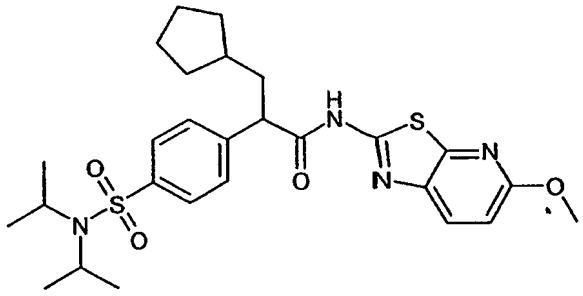
2-[4-(2-Carbamoyl-ethylsulfamoyl)-phenyl]-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide



The title compound is prepared analogously to Example 1: MS e/z (ES) 532.1 ($M+1^+$, 100%); ^{1}H NMR ($CDCl_3$) δ 12.69 (s, 1H), 8.03 (d, J=8.8, 1H), 7.78 (d, J=8.4, 2H), 7.62 (d, J=8.0, 2H), 7.23 (s,2H), 6.89 (d, J=8.8, 1H), 6.82 (s, 1H), 4.07 (t, J=7.6, 1H), 3.91 (s, 3H), 2.85-2.94 (m, 2H), 2.21 (t, J=7.2, 2H), 2.23-2.29 (m, 1H), 2.14-2.20 (m, 1H), 1.68-1.85 (m, 2H), 1.55-1.64 (m, 3H), 1.42-1.48 (m, 2H), 1.11-1.18 (m, 2H).

Example 9

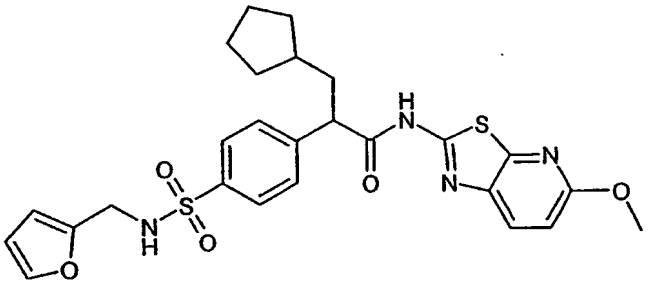
3-Cyclopentyl-2-(4-diisopropylsulfamoyl-phenyl)-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide



The title compound is prepared analogously to Example 1: MS e/z (ES) 545.5 ($M+1^+$, 100%); m.p. 83-85°C; ^{1}H NMR ($CDCl_3$) δ 12.68 (s, 1H), 8.02 (d, J=8.8, 1H), 7.81 (d, J=8.4, 2H), 7.59 (d, J=8.4, 2H), 6.90 (d, J=8.8,1H), 4.05 (t, J=7.6, 1H), 3.90 (s, 3H), 3.69 (m, 2H), 2.11-2.17 (m, 1H), 1.76-1.80 (m, 1H), 1.68-1.70 (m, 2H), 1.55-1.61 (m, 3H), 1.40-1.44 (m, 2 H), 1.22-1.24 (m, 1H), 1.15 (d, J=6.8,12H), 0.83-0.85 (m, 1H).

Example 10

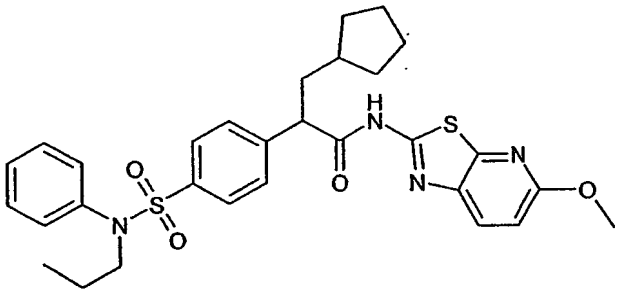
3-Cyclopentyl-2-{4-[(furan-2-ylmethyl)-sulfamoyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide



The title compound is prepared analogously to Example 1: MS e/z (ES) 541 ($M+1^+$, 100%); m.p. 244-247°C; ^1H NMR ($CDCl_3$) δ 12.66 (s, 1H), 8.15 (m, 1H), 8.03 (d, J=8.8, 1H), 7.73 (d, J=8.0, 2H), 7.56 (d, J=8.0, 2H), 7.37 (s, 1H), 6.92 (d, J=8.8,1H), 6.16 (s, 1H), 6.08 (s, 1H), 4.00 (m, 3H), 3.90 (s, 3H), 2.11-2.14 (m, 1H), 1.70-1.83 (m, 3H), 1.50-1.60 (m, 2H), 1.40-1.45 (m, 2H), 1.10-1.16 (m, 3H).

Example 11

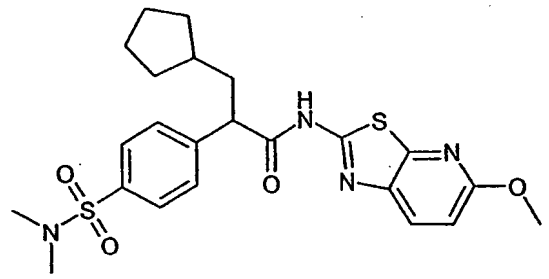
3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(phenyl-propyl-sulfamoyl)-phenyl]-propionamide



The title compound is prepared analogously to Example 1: MS e/z (ES) 579 ($M+1^+$, 100%); m.p. 83-85°C; ^1H NMR ($CDCl_3$) δ 12.69 (s, 1H), 8.03 (d, J=8.8, 1H), 7.55-7.61 (m, 4H), 7.28-7.35 (m, 2H), 7.03-7.05 (m, 2 H), 6.91 (d, J=8.8, 1H), 4.07 (t, J=7.2, 1H), 3.91 (s, 3H), 3.48-3.52 (t, J=6.8, 2H), 2.12-2.19 (m, 1H), 1.69-1.82 (m, 3H), 1.56-1.61 (m, 3 H), 1.43-1.46 (m, 2H), 1.27-1.33 (m, 3H), 1.12-1.14 (m, 2H), 0.79-0.83 (t, J=7.2, 3H).

Example 12

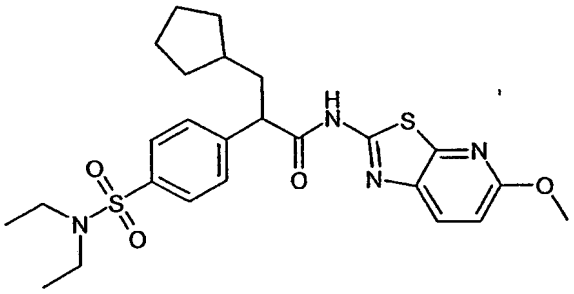
3-Cyclopentyl-2-(4-dimethylsulfamoyl-phenyl)-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide



The title compound is prepared analogously to Example 1: MS e/z (ES) 487 (M-1$^-$, 100%); m.p. 229-234°C; ^{1}H NMR ($CDCl_3$) δ 12.70 (s, 1H), 8.03 (d, J=8.8, 1H), 7.75 (d, J=8.4, 2H), 7.67 (d, J=8.4, 2H), 6.91 (d, J=8.8, 1H), 4.09 (t, J= 7.6 1H), 3.91 (s, 3H), 2.60 (s, 6H), 2.14-2.21 (m, 1H), 1.68-1.83 (m, 3H), 1.50-1.65 (m, 3H), 1.40-1.48 (m, 2H), 1.08-1.18 (m, 2H).

Example 13

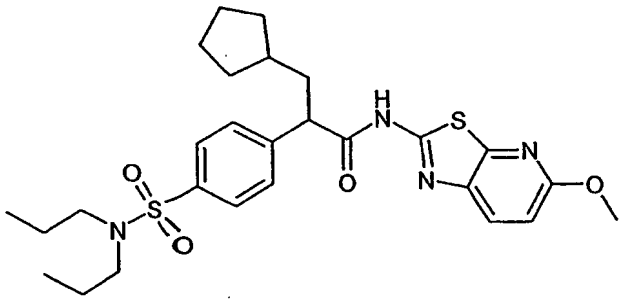
3-Cyclopentyl-2-(4-diethylsulfamoyl-phenyl)-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide



The title compound is prepared analogously to Example 1: MS e/z (ES) 515 (M-1$^-$, 100%); m.p. 150-152°C; ^{1}H NMR ($CDCl_3$) δ 12.69 (s, 1H), 8.03 (d, J=8.8, 1H), 7.78 (d, J=8.0, 2H), 7.61 (d, J=8.0, 2 H), 6.91 (d, J=8.8, 1H), 4.06 (t, J=7.6, 1H), 3.90 (s, 3H), 3.12 (q, J=7.2, 4H), 2.10-2.21 (m, 1H), 1.68-1.90 (m, 3H), 1.50-1.65 (m, 3H), 1.40-1.48 (m, 2H), 1.08-1.20 (m, 2H), 1.00-1.06 (m, 6H),

Example 14

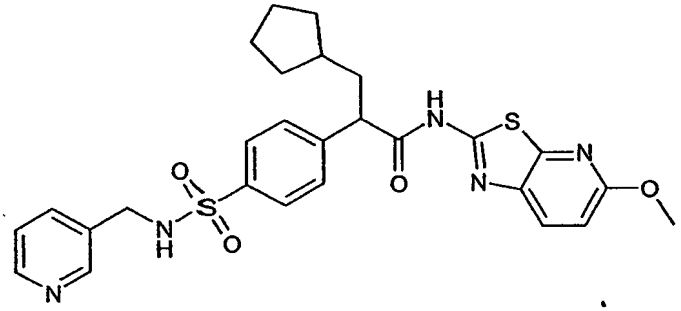
3-Cyclopentyl-2-(4-dipropylsulfamoyl-phenyl)-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide



The title compound is prepared analogously to Example 1: MS e/z (ES) 545 ($M+1^+$, 100%); m.p. 64-66°C; ^1H NMR ($CDCl_3$) δ 12.67 (s, 1H), 8.03 (d, J=8.8, 1H), 7.79 (d, J=8.4, 2H), 7.62 (d, J=8.4, 2H), 6.90 (d, J=8.8,1H), 4.07 (t, J=7.2,1H), 3.90 (s, 3H), 2.99 (t, J=7.2, 4H), 2.10-2.20 (m, 1H), 1.68-1.84 (m, 3H), 1.54-1.62 (m, 3H), 1.35-1.51 (m, 6H), 1.08-1.16 (m, 2H), 0.74-0.81 (m, 6H).

Example 15

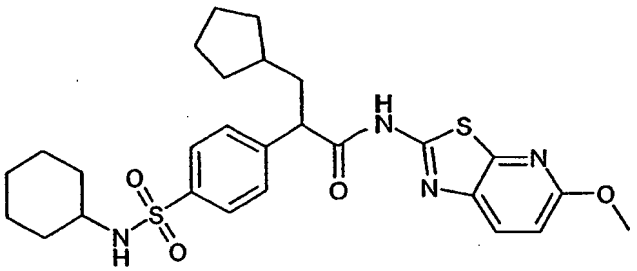
3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-{4-[(pyridin-3-ylmethyl)-sulfamoyl]-phenyl}-propionamide



The title compound is prepared analogously to Example 1: MS e/z (ES) 550 ($M-1^-$, 100%); m.p. 227-229°C; ^1H NMR ($CDCl_3$) δ 12.67 (s, 1H), 8.38 (s, 1H), 8.25-8.32 (m, 2H), 8.04 (d, J=8.4, 1H), 7.74 (d, J=8.0, 2H), 7.51-7.58 (m, 3H), 7.12-7.21 (m, 1H), 6.91 (d, J=8.8,1H), 4.02-4.06 (m, 3H), 3.91 (s, 3H), 2.10-2.18 (m, 1H), 1.70-1.83 (m, 3H), 1.60-1.80 (m, 3H), 1.40-1.50 (m, 2H), 1.10-1.22 (m, 2H).

Example 16

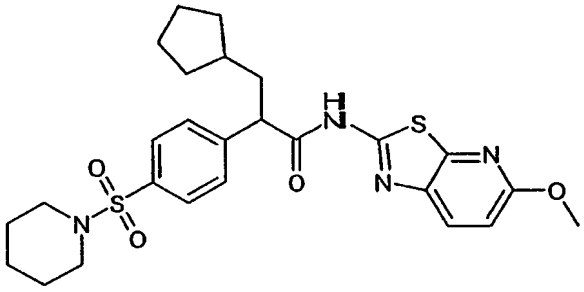
2-(4-Cyclohexylsulfamoyl-phenyl)-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide



The title compound is prepared analogously to Example 1: MS e/z (ES) 541.6 (M-1$^-$, 100%); m.p. 228-23°C; ^{1}H NMR ($CDCl_3$) δ 12.69 (s, 1H), 8.02 (d, J=8.8, 1H), 7.79 (d, J=8.4,2H), 7.59 (m, 3H), 6.91 (d, J=8.8, 1H), 4.05 (t, J=6.8,1H), 3.90 (s, 3H), 2.70-3.00 (m, 1H), 2.2-2.2 (m, 1H), 1.75-1.85 (m, 1H), 1.52-1.70 (m, 2H), 1.52-1.68 (m, 7H), 1.40-1.50 (m, 3H), 1.06-1.20 (m, 7H).

Example 17

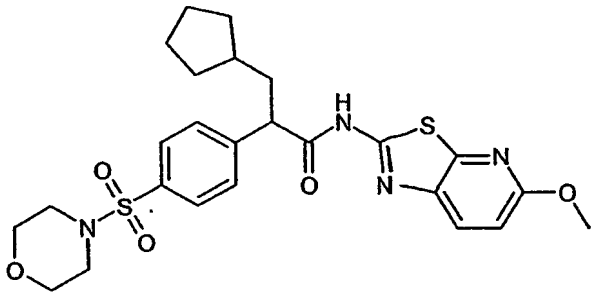
3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(piperidine-1-sulfonyl)-phenyl]-propionamide



The title compound is prepared analogously to Example 1: MS e/z (ES) 527 (M-1$^-$, 100%); m.p. 184-18°C; ^{1}H NMR ($CDCl_3$) δ 12.71 (s, 1H), 8.03 (d, J=8.8, 1H), 7.64-7.74 (m, 4 H), 6.91 (d, J=8.8, 1H), 4.08 (t, J=7.2, 1H), 3.90 (s, 3H), 2.86 (m, 5H) 2.13-2.21 (m, 1H), 1.63-1.76 (m, 3H), 1.45-1.60 (m, 8H), 1.39-1.43 (m, 2H), 1.07-1.21 (m, 2H).

Example 18

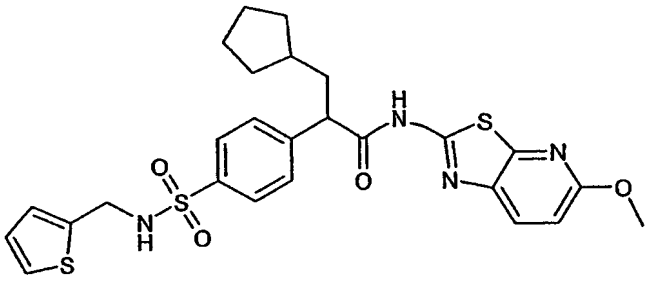
3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(morpholine-4-sulfonyl)-phenyl]-propionamide



The title compound is prepared analogously to Example 1: MS e/z (ES) 529 (M-1$^-$, 100%); m.p. 120-123°C; ^{1}H NMR ($CDCl_3$) δ 12.70 (s, 1H), 8.04 (d, J=8.4, 1H), 7.68-7.77 (m, 4 H), 6.91 (d, J=8.8, 1H), 4.11 (t, J=6.8, 1H), 3.91 (s, 3H), 3.61 (m, 4H), 2.85 (m, 4H), 2.16-2.20 (m, 1H), 1.79-1.83 (m, 1H), 1.72-1.78 (m, 2H), 1.5-1.70 (m, 3H), 1.40-1.44 (m, 2H), 1.08-1.20 (m, 2H).

Example 19

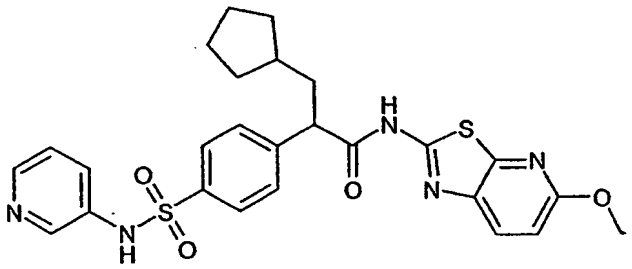
3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-{4-[(thiophen-2-ylmethyl)-sulfamoyl]-phenyl}-propionamide



The title compound is prepared analogously to Example 1: MS e/z (ES) 555 (M-1$^-$, 100%); m.p. 263-268°C; ^{1}H NMR ($CDCl_3$) δ 8.18 (s, 1H),7.70 (d, J=8.0 2H), 7.55-7.61 (m, 3H), 7.34 (d, J=3.6, 1H), 6.87 (m, 2H), 6.61 (d, J=8.4, 1H), 4.14 (s, 2H), 3.83 (s, 3H), 3.68 (t, 1H), 2.04-2.11 (m, 1H), 1.68-1.74 (m, 3H), 1.50-1.65 (m, 3H), 1.37-1.45 (m, 2H), 1.10-1.20 (m, 2H).

Example 20

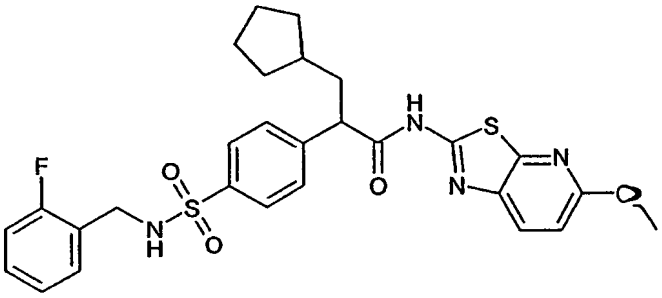
3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(pyridin-3-ylsulfamoyl)-phenyl]-propionamide



The title compound is prepared analogously to Example 1: MS e/z (ES) 536 (M-1⁻, 100%); m.p. 125-127°C; ^{1}H NMR ($CDCl_3$) δ 12.66 (s, 1H), 10.58 (s, 1H), 8.20-8.28 (m, 2H), 8.02 (d, J=8.8, 1H), 7.77 (d, J=8.0, 2H), 7.58 (d, J=8.0, 2 H), 7.46-7.51 (m, 1H), 7.21-7.30 (m, 1H), 6.90 (d, J=8.8,1H), 4.01 (m, 1H), 3.90 (s, 3H), 2.08-2.18 (m, 1H), 1.60-1.80 (m, 3H), 1.50-1.68 (m, 3H), 1.40-1.48 (m, 2H), 1.10-1.22 (m, 2H).

Example 21

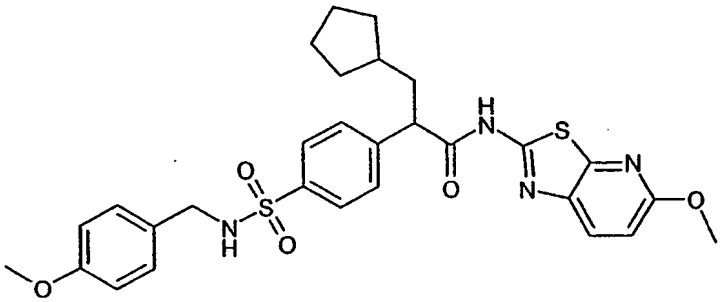
3-Cyclopentyl-2-[4-(2-fluoro-benzylsulfamoyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide



The title compound is prepared analogously to Example 1: MS e/z (ES) 567 (M-1⁻, 100%); m.p. 238-240°C; ^{1}H NMR ($CDCl_3$) δ 12.67 (s, 1H), 8.19 (t, J=5.6, 1H), 8.02 (d, J=8.8,1H), 7.73 (d, J=8.0, 2 H), 7.54 (d, J=8.0, 2H), 7.24 (t, J=6.4, 1H), 7.00-7.18 (m, 1H), 6.96-7.09 (m, 2H), 6.91 (d, J=8.8, 1H), 4.04 (m, 3H) 3.91 (s, 3H), 2.08-2.18 (m, 1H), 1.60-1.90 (m, 3H), 1.50-1.68 (m, 3H), 1.40-1.48 (m, 2H), 1.10-1.22 (m, 2H).

Example 22

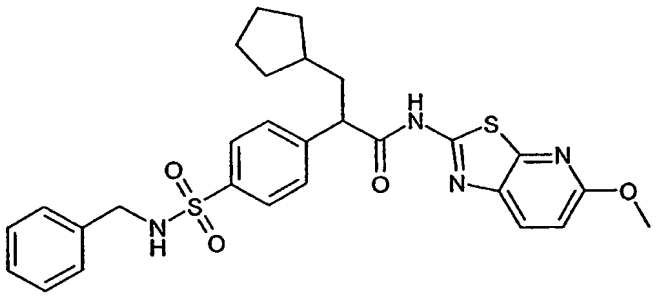
3-Cyclopentyl-2-[4-(4-methoxy-benzylsulfamoyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide



The title compound is prepared analogously to Example 1: MS e/z (ES) 565 (M-1$^-$, 100%); m.p. 170-172°C; ^{1}H NMR ($CDCl_3$) δ 12.64 (s, 1H), 9.91 (s, 1H), 8.02 (d, J=8.8, 1H), 7.67 (d, J=8.0, 2H), 7.54 (d, J=8.4, 2H), 6.91 (d, J=8.8, 2H), 6.63-6.78 (m, 3H), 3.95-4.04 (m, 1H), 3.91 (s, 3H), 3.63 (s, 3H), 2.10-2.18 (m, 1H), 1.70-1.83 (m, 3H), 1.60-1.80 (m, 3H), 1.40-1.50 (m, 2H), 1.10-1.22 (m, 2H).

Example 23

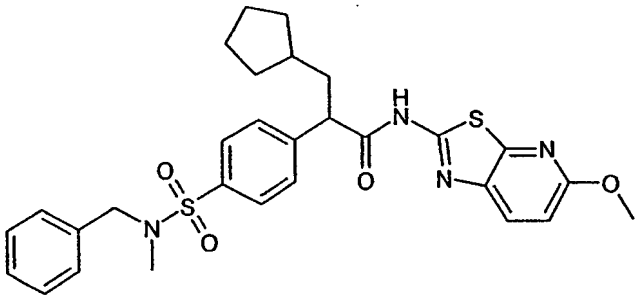
2-(4-Benzylsulfamoyl-phenyl)-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide



The title compound is prepared analogously to Example 1: MS e/z (ES) 549 (M-1$^-$, 100%); m.p. 237-240°C; ^{1}H NMR ($CDCl_3$) δ 12.68 (s, 1H), 8.16 (t, J=6.4, 1H), 8.02 (d, J=8.8,1H), 7.74 (d, J=8.4, 2 H), 7.56 (d, J=8.4, 2H), 7.01-7.30 (t, 5H), 6.91 (d, J=8.8, 1H), 3.92-4.10 (m, 3H), 3.91 (s, 3H), 2.08-2.18 (m, 1H), 1.60-1.90 (m, 3H), 1.50-1.68 (m, 3H), 1.40-1.48 (m, 2H), 1.10-1.22 (m, 2H).

Example 24

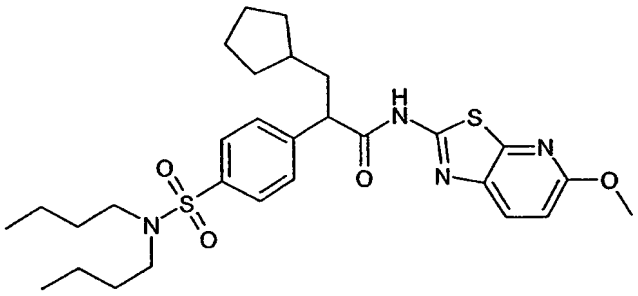
2-[4-(Benzyl-methyl-sulfamoyl)-phenyl]-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide



The title compound is prepared analogously to Example 1: MS e/z (ES) 565 ($M+1^+$, 100%); m.p. 206-208°C; ^{1}H NMR ($CDCl_3$) δ 12.73 (s, 1H), 8.04 (d, J=8.8, 1H), 7.85 (d, J=8.0, 2H),7.67 (d, J=8.0, 2H), 7.26-7.32 (m, 5H), 6.91 (d, J=8.8, 1H), 4.08-4.13 (m, 3H), 3.90 (s, 3H), 2.54 (s, 3H), 2.14-2.21 (m, 1H), 1.71-1.82 (m, 3H), 1.50-1.65 (m, 3H), 1.40-1.49 (m, 2H), 1.10-1.25 (m, 2H).

Example 25

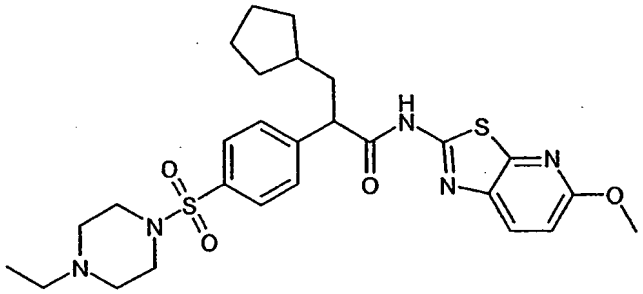
3-Cyclopentyl-2-(4-dibutylsulfamoyl-phenyl)-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide



The title compound is prepared analogously to Example 1: MS e/z (ES) 573.4 ($M+1^+$, 100%); m.p. 65-67°C; ^{1}H NMR ($CDCl_3$) δ 12.66 (s, 1H), 8.02 (d, J=8.8, 1H), 7.78 (d, J=8.4, 2H), 7.62 (d, J=8.4, 2H), 6.90 (d, J=8.8,1H), 4.06 (t, J=7.6, 1H), 3.90 (s, 3H), 3.04 (t, J=7.6, 4H), 2.10-2.15 (m, 1H), 1.79-1.85 (m, 1H), 1.65-1.76 (m, 2H), 1.55-1.60 (m, 3 H), 1.32-1.44 (m, 6H), 1.13-1.30 (m, 6H), 0.78-0.82 (m, 6H).

Example 26

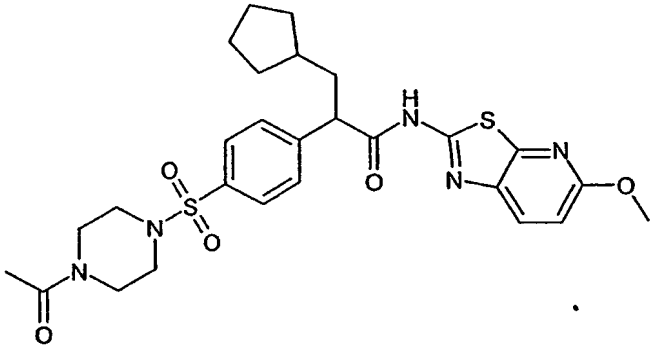
3-Cyclopentyl-2-[4-(4-ethyl-piperazine-1-sulfonyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide



The title compound is prepared analogously to Example 1: MS e/z (ES) 556 ($M-1^-$, 100%); m.p. 106-10°C; ^{1}H NMR ($CDCl_3$) δ 12.71 (s, 1H), 8.03 (d, J=8.8, 1H), 7.66-7.75 (m, 4H), 6.91 (d, J=8.4, 1H), 4.09 (t, J=7.6, 1H), 3.91 (s, 3H), 2.85-2.88 (m, 4H), 2.34-2.38 (m, 4H), 2.23-2.29 (m, 2H), 2.14-2.21 (m, 1H), 1.70-1.83 (m, 3H), 1.55-1.61 (m, 3H), 1.42-1.45(m, 2H), 1.11-1.18 (m, 2H), 0.86-0.91 (m, 3H).

Example 27

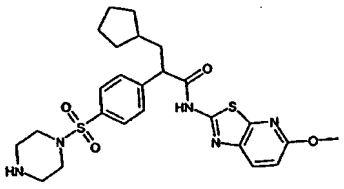
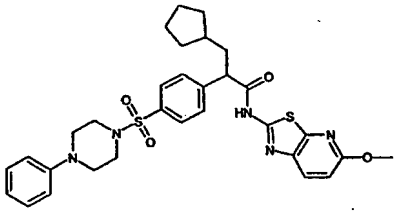
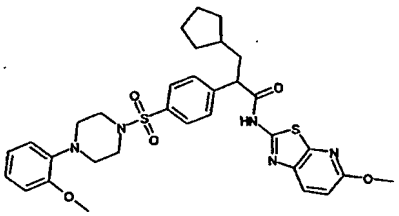
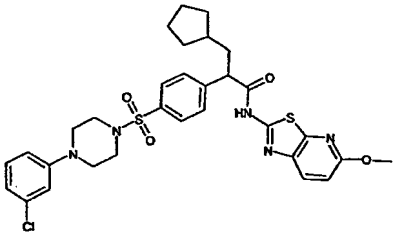
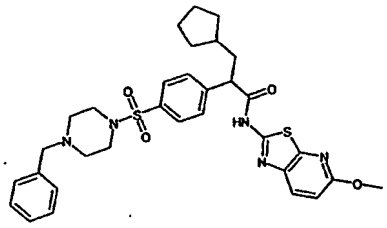
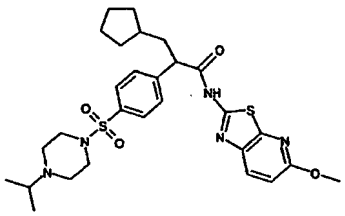
2-[4-(4-Acetyl-piperazine-1-sulfonyl)-phenyl]-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide

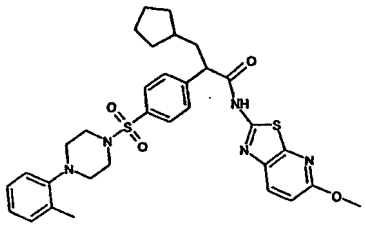
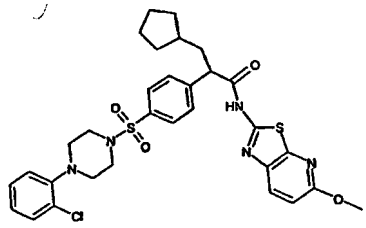
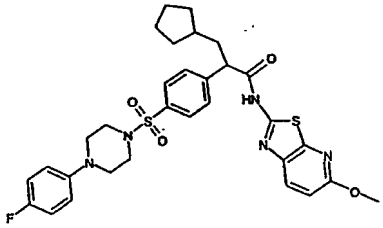
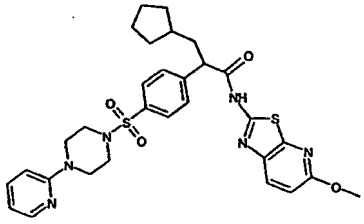
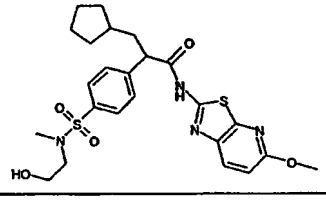
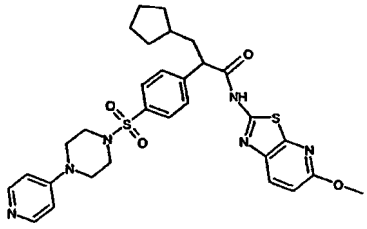


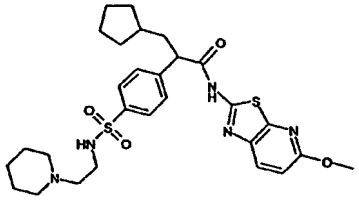
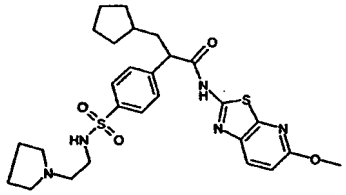
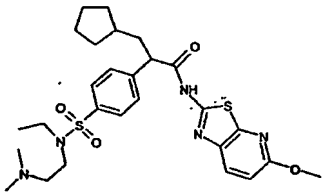
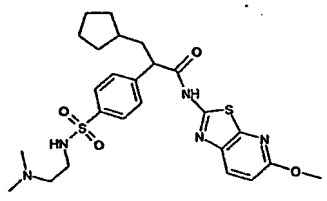
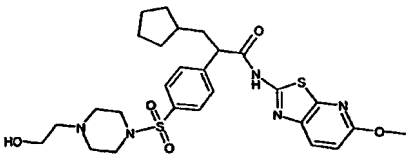
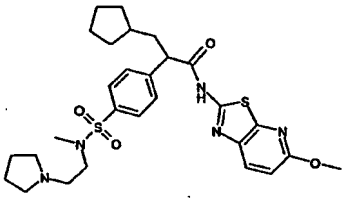
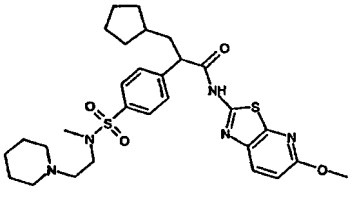
The title compound is prepared analogously to Example 1: MS e/z (ES) 572 ($M+1^+$, 100%); m.p. 215-217°C; ^{1}H NMR ($CDCl_3$) δ 12.72 (s, 1H), 8.03 (d, J=8.8, 1H), 7.66-7.76 (m, 4H), 6.91 (d, J=8.4, 1H), 4.09 (m, 1H), 3.90 (s, 3H), 3.47-3.50 (m, 4H), 2.84-2.91 (m, 4H), 2.14-2.20 (m, 1H), 1.91 (s, 3H), 1.70-1.81 (m, 2H), 1.50-1.59 (m, 3H), 1.40-1.49 (m, 2H), 1.08-1.14 (m, 3H).

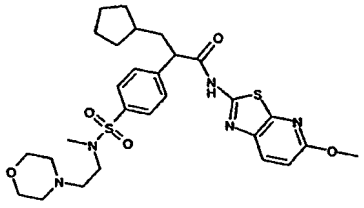
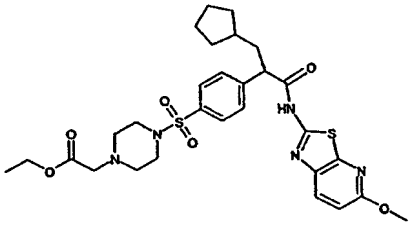
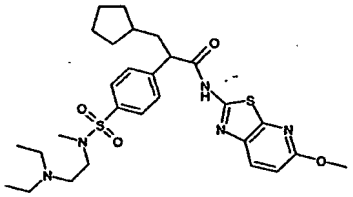
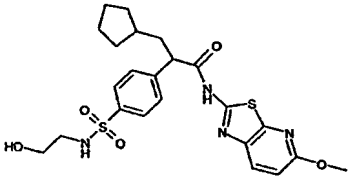
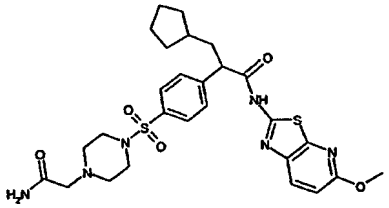
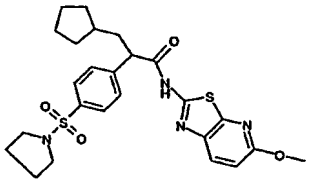
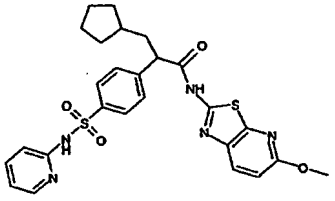
The following compounds may also be prepared according to Method A.

Example 28

Example	Structure	Chemical Name	MS; M+1$^+$
28-1		3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(piperazine-1-sulfonyl)-phenyl]-propionamide hydrochloride	530.68
28-2		3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(4-phenyl-piperazine-1-sulfonyl)-phenyl]-propionamide	606.78
28-3		3-Cyclopentyl-2-{4-[4-(2-methoxy-phenyl)-piperazine-1-sulfonyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide	636.81
28-4		2-{4-[4-(3-Chloro-phenyl)-piperazine-1-sulfonyl]-phenyl}-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide	641.23
28-5		2-[4-(4-Benzyl-piperazine-1-sulfonyl)-phenyl]-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide	620.81
28-6		3-Cyclopentyl-2-[4-(4-isopropyl-piperazine-1-sulfonyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide	572.77

Example	Structure	Chemical Name	MS; M+1$^+$
28-7		3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(4-o-tolyl-piperazine-1-sulfonyl)-phenyl]-propionamide	620.81
28-8		N-[2-(2-{4-[4-(2-Chloro-phenyl)-piperazine-1-sulfonyl]-phenyl}-3-cyclopentyl-propionylamino)-thiazol-5-yl]-acetimidic acid methyl ester	641.23
28-9		3-Cyclopentyl-2-{4-[4-(4-fluoro-phenyl)-piperazine-1-sulfonyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide	624.77
28-10		3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(4-pyridin-2-yl-piperazine-1-sulfonyl)-phenyl]-propionamide	607.77
28-11		3-Cyclopentyl-2-{4-[(2-hydroxy-ethyl)-methyl-sulfamoyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide	519.66
28-12		3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(4-pyridin-4-yl-piperazine-1-sulfonyl)-phenyl]-propionamide	607.77

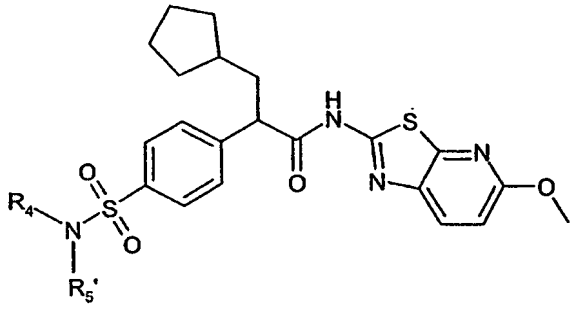
Example	Structure	Chemical Name	MS; M+1$^+$
28-13		3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(2-piperidin-1-yl-ethylsulfamoyl)-phenyl]-propionamide	572.77
28-14		3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(2-pyrrolidin-1-yl-ethylsulfamoyl)-phenyl]-propionamide	558.74
28-15		3-Cyclopentyl-2-{4-[(2-dimethylamino-ethyl)-ethyl-sulfamoyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide hydrochloride	560.76
28-16		3-Cyclopentyl-2-[4-(2-dimethylamino-ethylsulfamoyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide hydrochloride	532.7
28-17		3-Cyclopentyl-2-{4-[4-(2-hydroxy-ethyl)-piperazine-1-sulfonyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide	574.74
28-18		3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-{4-[methyl-(2-pyrrolidin-1-yl-ethyl)-sulfamoyl]-phenyl}-propionamide hydrochloride	572.77
28-19		3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-{4-[methyl-(2-piperidin-1-yl-ethyl)-sulfamoyl]-phenyl}-propionamide hydrochloride	586.79

Example	Structure	Chemical Name	MS; M+1$^+$
28-20		3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-{4-[methyl-(2-morpholin-4-yl-ethyl)-sulfamoyl]-phenyl}-propionamide	588.77
28-21		4-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-piperazin-1-yl)-acetic acid ethyl ester	616.78
28-22		3-Cyclopentyl-2-{4-[(2-diethylamino-ethyl)-methyl-sulfamoyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide	574.78
28-23		3-Cyclopentyl-2-[4-(2-hydroxy-ethylsulfamoyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide	505.63
28-24		2-[4-(4-Carbamoylmethyl-piperazine-1-sulfonyl)-phenyl]-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide	587.74
28-25		3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(pyrrolidine-1-sulfonyl)-phenyl]-propionamide	515.67
28-26		3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(pyridin-2-ylsulfamoyl)-phenyl]-propionamide	538.66

The following compounds may be prepared according to Method B:

Example 29

4-[2-cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonamide of the formula



A. 3-Cyclopentyl-2-(4-nitro-phenyl)-propionic acid ethyl ester

To a 1 L round bottom flask containing 250 mL of 9:1 THF/DMPU at -78C is added under nitrogen 11 mL (78.6 mmol) anhydrous DIEA followed by rapid addition of 32 mL of 2.5M n-BuLi in hexanes. After 10 min at -78°C a solution of 15.4 g (74 mmol) of p-nitro-phenylacetic acid, ethyl ester in 100 mL of 9:1 THF/DMPU is added dropwise over 30 min. A deep purple solution results, and the reaction mixture is stirred at -78°C for 30 min and then cyclopentyl methyl iodide (17.6 g, 78 mmol) in 50 mL of 9:1 THF/DMPU is added. The reaction is stirred while warming slowly to RT temperature overnight. The mixture is poured into 1 L of 1N HCl (aq) and extracted twice with methyl-t-butylether (MTBE). The combined MTBE extracts are washed with brine, dried over anhydrous magnesium sulfate, filtered and reduced to an orange oil. Flash chromatography over silica eluting with 4:1 hexane/MTBE affords 3-cyclopentyl-2-(4-nitro-phenyl)-propionic acid ethyl ester as an orange oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.0-1.1 (m, 2H), 1.2 (t, 3H, J=7.2), 1.4-1.8 (m, 5H), 1.8-1.9 (m, 2H), 2.1-2.25 (m, 2H), 3.74 (t, 1H, J=7.8), 4.1 (m, 2H), 7.51 (d, 2H, J=8.8), 8.19 (d, 2H, J=8.8).

B. 3-Cyclopentyl-2-(4-nitro-phenyl)-propionic acid

The title A compound , 3-cyclopentyl-2-(4-nitro-phenyl)-propionic acid ethyl ester (3.6 g, 12.3 mmol) is dissolved in 25 mL of methanol and aqueous NaOH (0.70 g, 17.5 mmol in 4 mL of water) is added and the mixture is stirred at RT overnight. The methanol is removed under reduced pressure and the residue is diluted with 100 mL of water and extracted with ether. The aqueous layer is then acidified with 1N HCl (aq) and then extracted with ethyl acetate. The combined ethyl acetate layers are dried over anhydrous magnesium sulfate , filtered and reduced under vacuum to a crude orange oil. The crude oil is triturated with 100 mL of

hexane/10-15mL of ether to produce 3-cyclopentyl-2-(4-nitro-phenyl)-propionic acid as a solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.0-1.1 (m, 2H), 1.4-1.8 (m, 5H), 1.8-1.9 (m, 2H), 2.1-2.25 (m, 2H), 3.74 (t, 1H, J=7.8), 7.51 (d, 2H, J=8.8), 8.19 (d, 2H, J=8.8).

C. 3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-(4-nitro-phenyl)-propionamide

The title B compound, 3-cyclopentyl-2-(4-nitro-phenyl)-propionic acid (7.5 g, 28.5 mmol) is dissolved in 25mL of thionyl chloride and a drop of DMF and the mixture stirred at RT for 5-6 h. The excess of thionyl chloride is removed under reduced pressure. The residue is then taken up in DCM and added dropwise to a solution of 5.2 g (28.5 mmol) of the aminothiazole in 25 mL pyridine. The reaction mixture is stirred for 5 h before being evaporated to remove the pyridine. The residue is partitioned between ethyl acetate and brine, extracted with ethyl acetate. The combined organic layers are washed with saturated sodium bicarbonate, brine, dried over anhydrous magnesium sulfate, filtered and then reduced to an orange-brown solid. This is then vacuum dried to afford 3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-(4-nitro-phenyl)-propionamide as a foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.0-1.1 (m, 2H), 1.4-1.8 (m, 5H), 1.8-1.9 (m, 2H), 2.1-2.25 (m, 2H), 3.6 (t, 1H, J=7.8), 4.01 (s, 3H), 6.8 (d, 1H, J=8.8), 7.4 (d, 2H, J=8.6), 7.8 (d, 1H, J=8.8 Hz), 8.19 (d, 2H, J=8.6 Hz), 9.3 (s, 1H).

D. 2-(4-Amino-phenyl)-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide

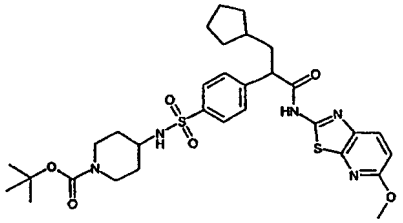
The title C compound, 3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-(4-nitro-phenyl)-propionamide (12 g, 28.2 mmol) is diluted with 160 mL of ethanol and 150 mL acetic acid. 8 g of iron powder (325 mesh, 0.14 mol) is added and the mixture heated to reflux. Once reflux begins the mixture is stirred vigorously and then heating is discontinued and the mixture is allowed to cool slowly. The solvents are removed and the residue is treated with 250 mL of water. Saturated sodium bicarbonate ia added carefully to bring the mixture to a pH of 8-9. The mixture is extracted with ethyl acetate, washed with brine, dried and evaporated to give an orange solid which is triturated from hexane. The resulted solid is collected by filtration to afford 2-(4-amino-phenyl)-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.0-1.1 (m, 2H), 1.4-1.8 (m, 5H), 1.8-1.9 (m, 2H), 2.1-2.25 (m, 2H), 3.6 (t, 1H, J=7.8), 3.98 (s, 3H), 6.7 (d, 1H, J=8.8), 6.8 (d, 2H, J=8.6), 7.2 (d, 2H, J=8.6), 7.8 (d, 1H, J=8.8).

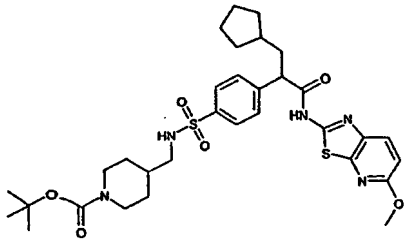
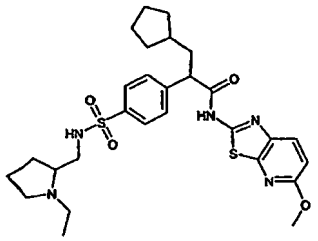
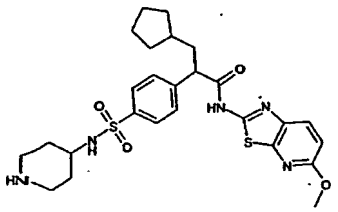
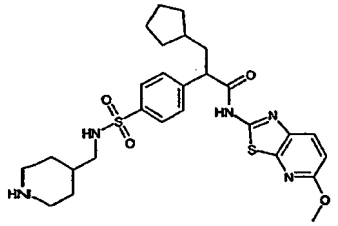
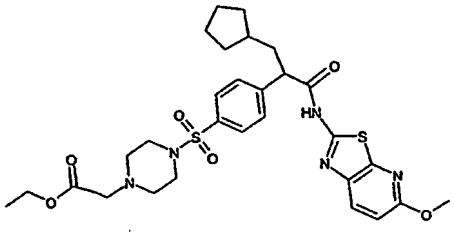
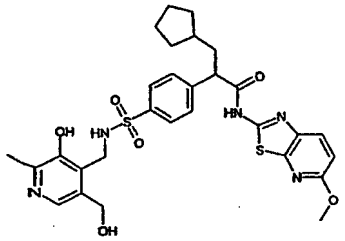
E. 4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl chloride

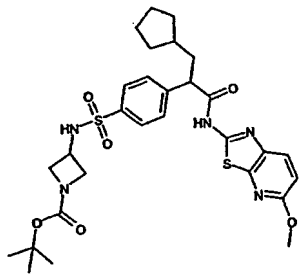
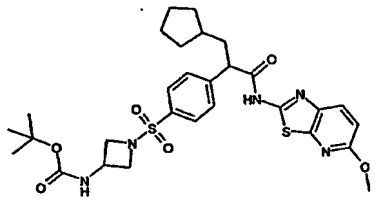
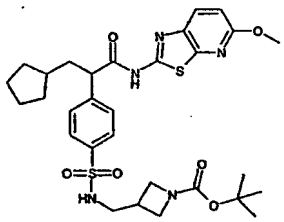
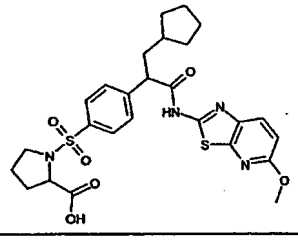
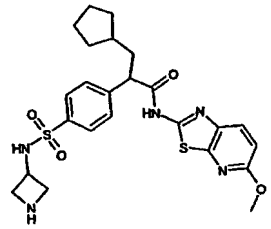
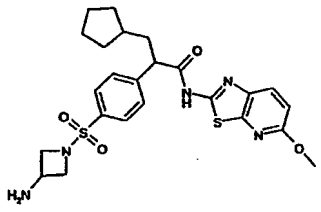
The title D compound, 2-(4-amino-phenyl)-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide (2.0 g, 5.1 mmol) is dissolved in 50 mL of acetic acid and 20 mL of concentrated HCl and the mixture is cooled to 0°C. A solution of 0.35 g (5.1 mmol) of $NaNO_2$ in 5 mL of water is added dropwise and the mixture is stirred for 30 min. The resulting yellow solution is then added to 180 mL of the Green Solution (prepared by bubbling 74 g of sulfur dioxide gas into 740 mL of glacial acetic acid followed by addition of 30 g of $CuCl_2$ in 35-40 mL water. The resulting mixture is filtered through filter paper to obtain a clear green solution) and the mixture is stirred at RT overnight (the initial black-green solution transforms to a light green solution after 24 h). The resulting mixture is poured onto 500 g of ice and the precipitated solids are collected by filtration, washed with water and then dissolved in ethyl acetate, washed with brine, dried over anhydrous magnesium sulfate, filtered and evaporated to afford a yellow foam. This material is flash chromatographed over silica eluting with 7:3 hexane/ethyl acetate to afford 4-[2-cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl chloride as a stable yellow foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.0-1.1 (m, 2H), 1.4-1.8 (m, 5H), 1.8-1.9 (m, 2H), 2.1-2.25 (m, 2H), 3.7 (t, 1H, J=7.8), 4.01 (s, 3H), 6.8 (d, 1H, J=8.8), 7.5 (d, 2H, J=8.6), 7.8 (d, 1H, J=8.8), 8.19 (d, 2H, J=8.6), 9.3 (s, 1H).

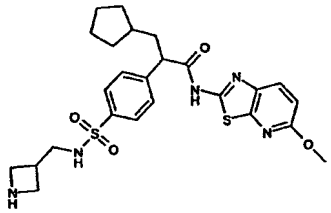
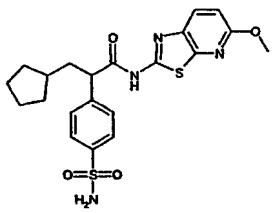
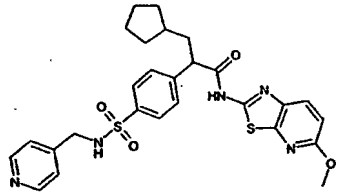
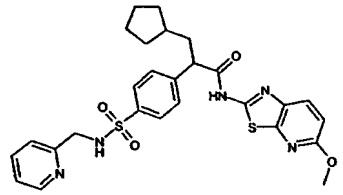
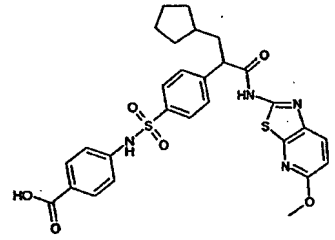
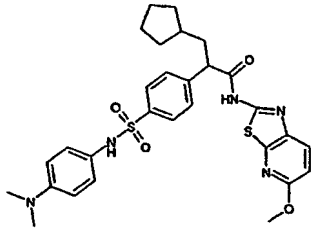
G. Coupling of 4-[2-cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl chloride with an amine of formula R_4-NH-R_5'

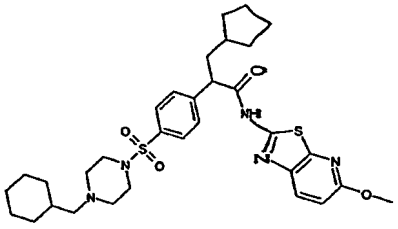
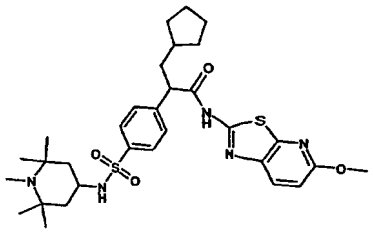
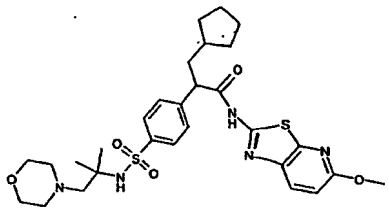
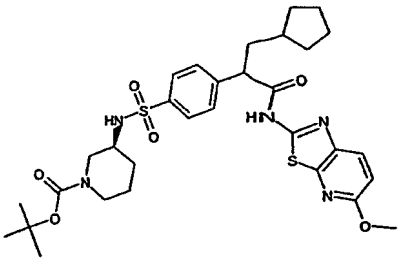
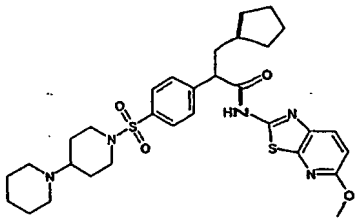
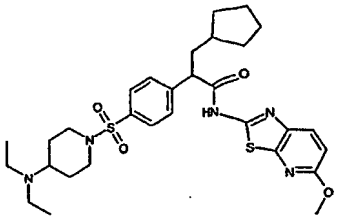
The title E compound, 4-[2-cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl chloride may be reacted with the desired amine of formula R_4-NH-R_5' according to methods well know in the art, e.g., using reaction conditions as described in Example 1 for the preparation of the title C compound.

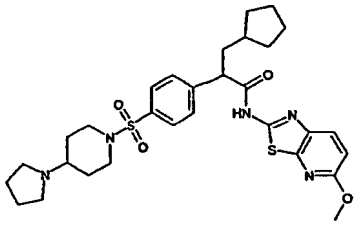
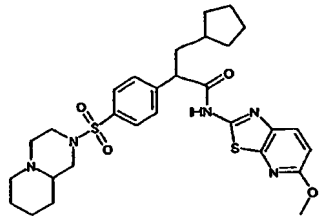
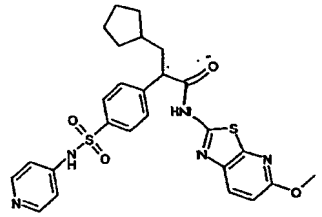
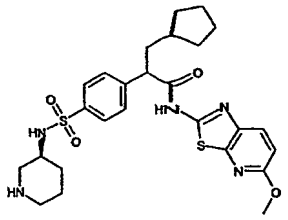
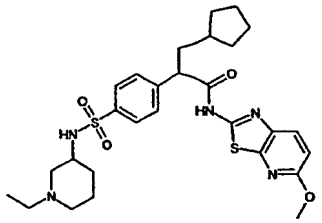
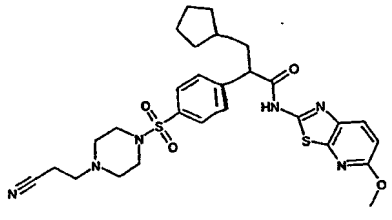
Example	Structure	Chemical name	MS; M+1$^+$
29-1		4-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonylamino}-piperidine-1-carboxylic acid tert-butyl ester	644.83

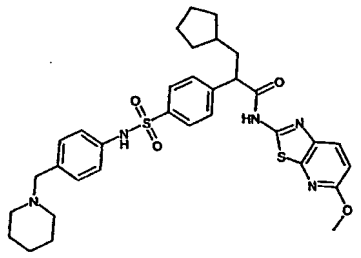
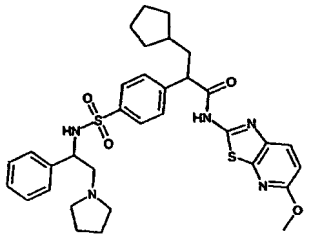
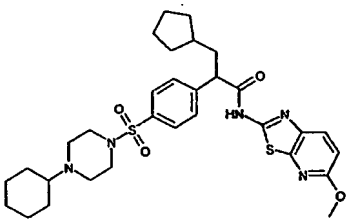
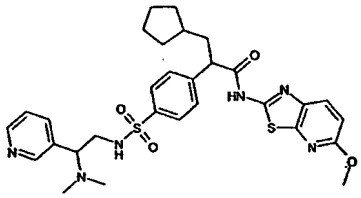
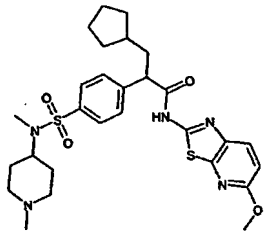
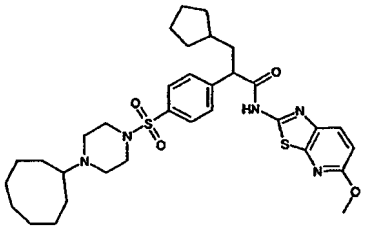
Example	Structure	Chemical name	MS; M+1$^+$
29-2		4-({4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonylamino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester	658.86
29-3		3-Cyclopentyl-2-{4-[(1-ethyl-pyrrolidin-2-ylmethyl)-sulfamoyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide	572.77
29-4		3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(piperidin-4-ylsulfamoyl)-phenyl]-propionamide	544.71
29-5		3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-{4-[(piperidin-4-ylmethyl)-sulfamoyl]-phenyl}-propionamide	558.74
29-6		(4-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-piperazin-1-yl)-acetic acid ethyl ester	616.78
29-7		3-Cyclopentyl-2-{4-[(3-hydroxy-5-hydroxymethyl-2-methyl-pyridin-4-ylmethyl)-sulfamoyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide	612.74

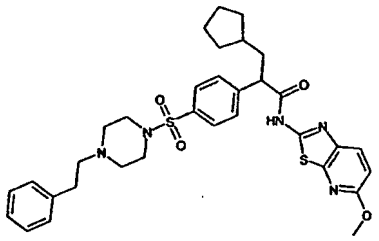
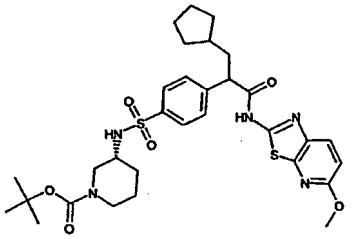
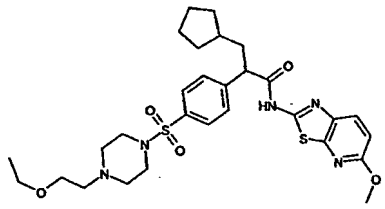
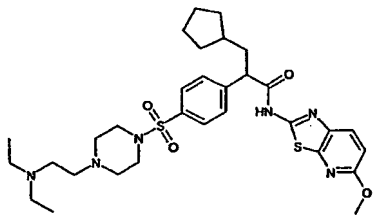
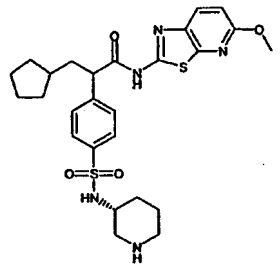
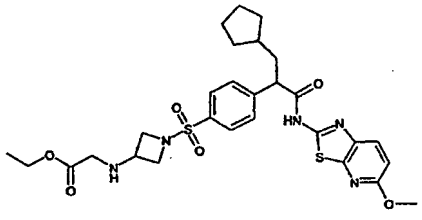
Example	Structure	Chemical name	MS; M+1$^+$
29-8		3-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonylamino}-azetidine-1-carboxylic acid tert-butyl ester	616.78
29-9		(1-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-azetidin-3-yl)-carbamic acid tert-butyl ester	616.78
29-10		3-({4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonylamino}-methyl)-azetidine-1-carboxylic acid tert-butyl ester	630.8
29-11		1-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-pyrrolidine-2-carboxylic acid	559.68
29-12		2-[4-(Azetidin-3-ylsulfamoyl)-phenyl]-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide	516.66
29-13		2-[4-(3-Amino-azetidine-1-sulfonyl)-phenyl]-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide	516.66

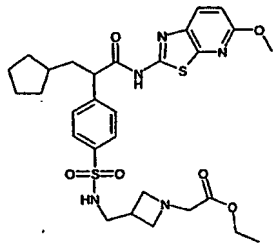
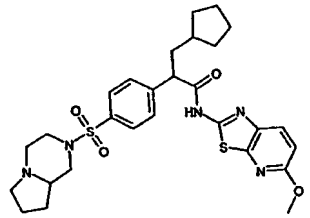
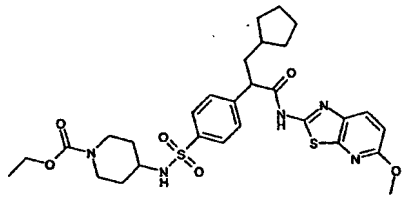
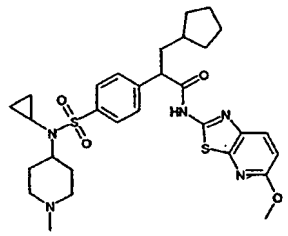
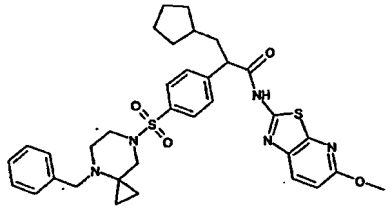
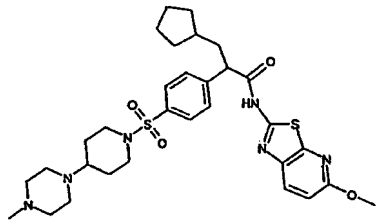
Example	Structure	Chemical name	MS; M+1$^+$
29-14		2-{4-[(Azetidin-3-ylmethyl)-sulfamoyl]-phenyl}-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide	530.68
29-15		3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-(4-sulfamoyl-phenyl)-propionamide	461.58
29-16		3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-{4-[(pyridin-4-ylmethyl)-sulfamoyl]-phenyl}-propionamide	552.69
29-17		3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-{4-[(pyridin-2-ylmethyl)-sulfamoyl]-phenyl}-propionamide	552.69
29-18		4-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonylamino}-benzoic acid	581.69
29-19		3-Cyclopentyl-2-[4-(4-dimethylamino-phenylsulfamoyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide	580.75

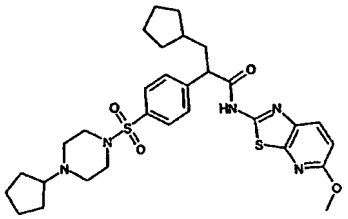
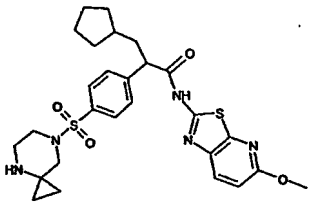
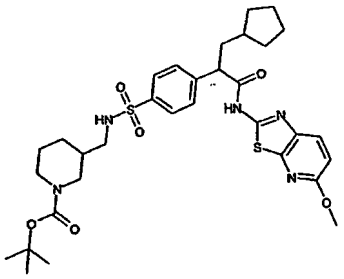
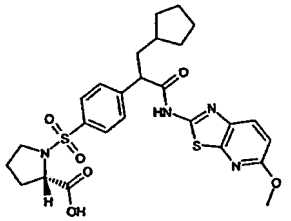
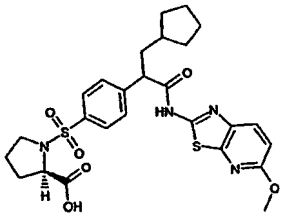
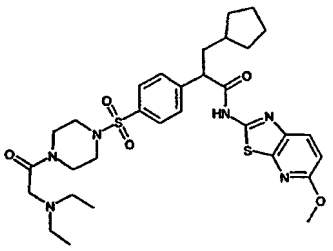
Example	Structure	Chemical name	MS; M+1$^+$
29-20		2-[4-(4-Cyclohexylmethyl-piperazine-1-sulfonyl)-phenyl]-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide	626.86
29-21		3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(1,2,2,6,6-pentamethyl-piperidin-4-ylsulfamoyl)-phenyl]-propionamide	614.85
29-22		3-Cyclopentyl-2-[4-(1,1-dimethyl-2-morpholin-4-yl-ethylsulfamoyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide	602.79
29-23		(S)-3-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonylamino}-piperidine-1-carboxylic acid tert-butyl ester	644.83
29-24		2-[4-([1,4']Bipiperidinyl-1'-sulfonyl)-phenyl]-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide	612.83
29-25		3-Cyclopentyl-2-[4-(4-diethylamino-piperidine-1-sulfonyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide	600.82

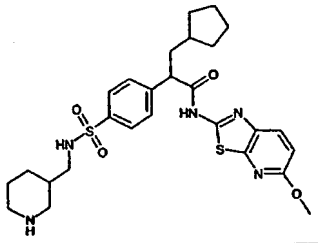
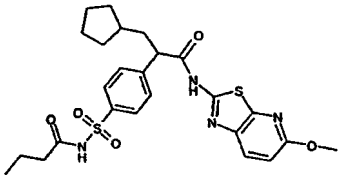
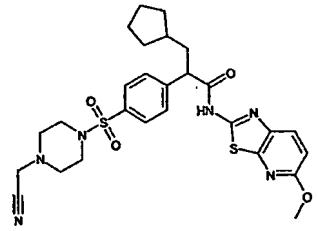
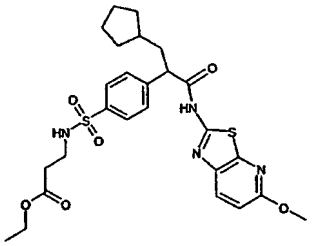
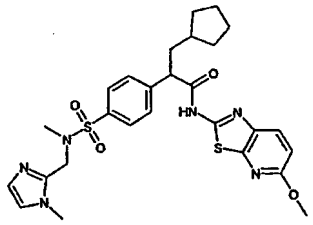
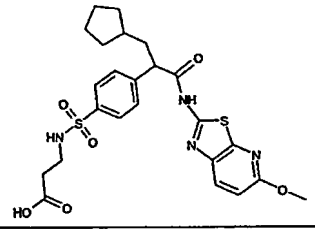
Example	Structure	Chemical name	MS; M+1$^+$
29-26		3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(4-pyrrolidin-1-yl-piperidine-1-sulfonyl)-phenyl]-propionamide	598.8
29-27		3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(octahydro-pyrido[1,2-a]pyrazine-2-sulfonyl)-phenyl]-propionamide	584.78
29-28		3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(pyridin-4-ylsulfamoyl)-phenyl]-propionamide	538.66
29-29		3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-((S)-piperidin-3-ylsulfamoyl)-phenyl]-propionamide	544.71
29-30		3-Cyclopentyl-2-[4-(1-ethyl-piperidin-3-ylsulfamoyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide	572.77
29-31		2-{4-[4-(2-Cyano-ethyl)-piperazine-1-sulfonyl]-phenyl}-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide	583.75

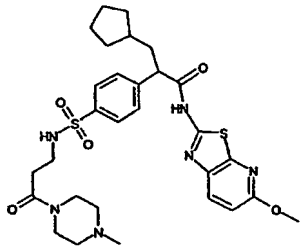
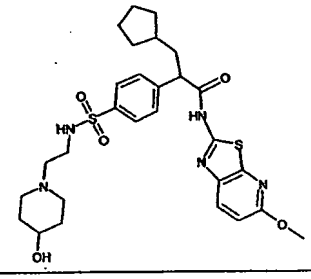
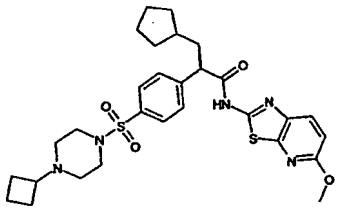
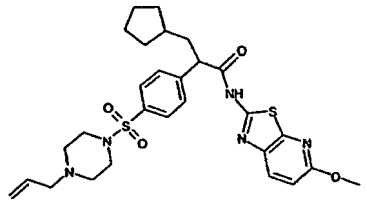
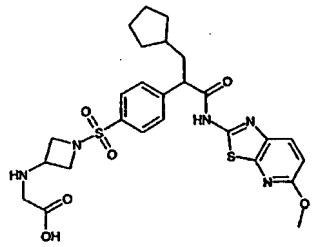
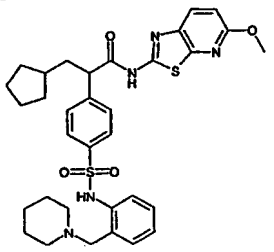
Example	Structure	Chemical name	MS; M+1$^+$
29-32		3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(4-piperidin-1-ylmethyl-phenylsulfamoyl)-phenyl]-propionamide	634.84
29-33		3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(1-phenyl-2-pyrrolidin-1-yl-ethylsulfamoyl)-phenyl]-propionamide	634.84
29-34		2-[4-(4-Cyclohexyl-piperazine-1-sulfonyl)-phenyl]-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide	612.83
29-35		3-Cyclopentyl-2-[4-(2-dimethylamino-2-pyridin-3-yl-ethylsulfamoyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide	609.79
29-36		3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-{4-[methyl-(1-methyl-piperidin-4-yl)-sulfamoyl]-phenyl}-propionamide	572.77
29-37		2-[4-(4-Cyclooctyl-piperazine-1-sulfonyl)-phenyl]-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide	640.89

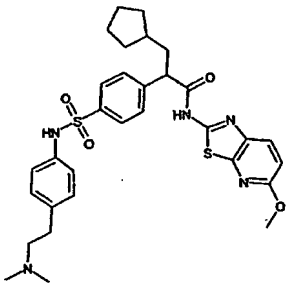
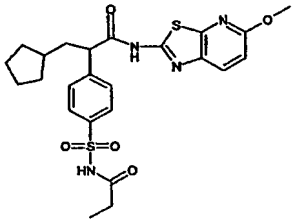
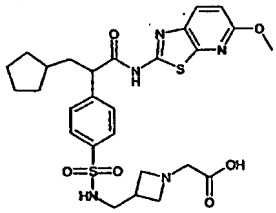
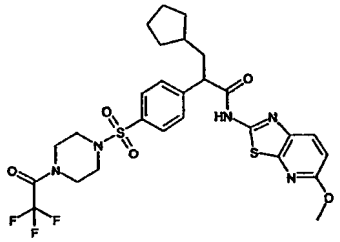
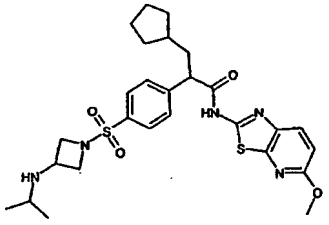
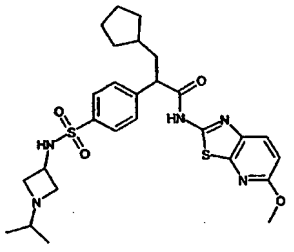
Example	Structure	Chemical name	MS; M+1$^+$
29-38		3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(4-phenethyl-piperazine-1-sulfonyl)-phenyl]-propionamide	634.84
29-39		(R)-3-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonylamino}-piperidine-1-carboxylic acid tert-butyl ester	644.83
29-40		3-Cyclopentyl-2-{4-[4-(2-ethoxy-ethyl)-piperazine-1-sulfonyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide	602.79
29-41		3-Cyclopentyl-2-{4-[4-(2-diethylamino-ethyl)-piperazine-1-sulfonyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide	629.86
29-42		3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-((R)-piperidin-3-ylsulfamoyl)-phenyl]-propionamide	544.71
29-43		(1-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-azetidin-3-ylamino)-acetic acid ethyl ester	602.75

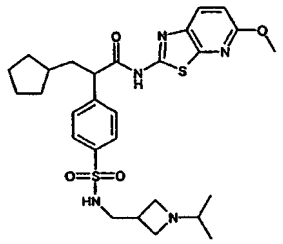
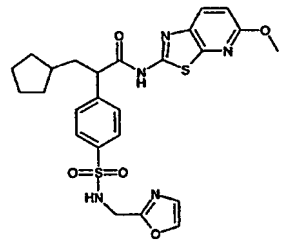
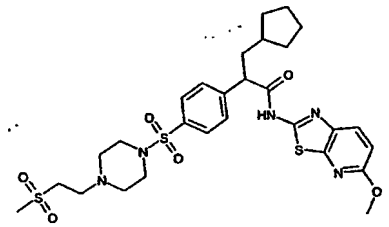
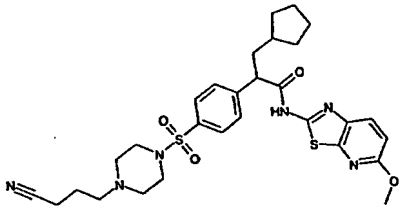
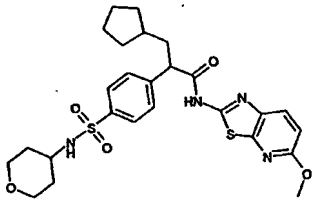
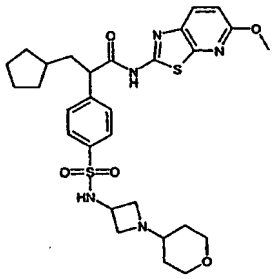
Example	Structure	Chemical name	MS; M+1+
29-44		[3-({4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonylamino}-methyl)-azetidin-1-yl]-acetic acid ethyl ester	616.78
29-45		3-Cyclopentyl-2-[4-(hexahydro-pyrrolo[1,2-a]pyrazine-2-sulfonyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide	570.75
29-46		4-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonylamino}-piperidine-1-carboxylic acid ethyl ester	616.78
29-47		3-Cyclopentyl-2-{4-[cyclopropyl-(1-methyl-piperidin-4-yl)-sulfamoyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide	598.8
29-48		2-[4-(4-Benzyl-4,7-diaza-spiro[2.5]octane-7-sulfonyl)-phenyl]-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide	646.85
29-49		3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-{4-[4-(4-methyl-piperazin-1-yl)-piperidine-1-sulfonyl]-phenyl}-propionamide	627.85

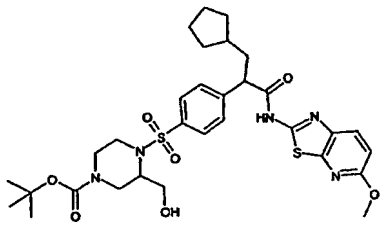
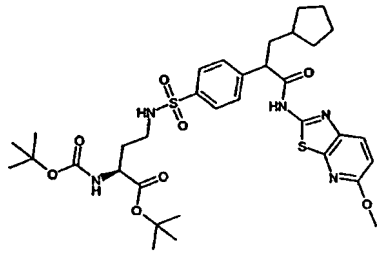
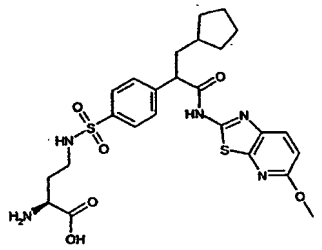
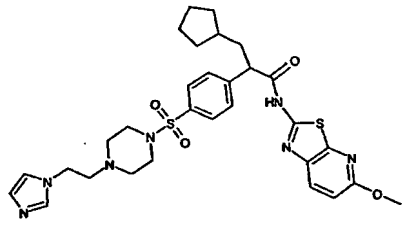
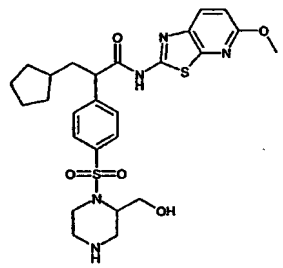
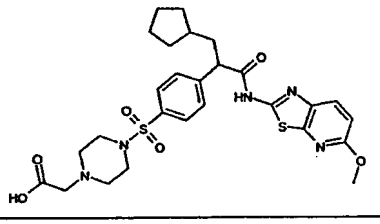
Example	Structure	Chemical name	MS; M+1$^+$
29-50		3-Cyclopentyl-2-[4-(4-cyclopentyl-piperazine-1-sulfonyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide	598.8
29-51		3-Cyclopentyl-2-[4-(4,7-diaza-spiro[2.5]octane-7-sulfonyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide	556.72
29-52		3-({4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonylamino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester	658.86
29-53		(S)-1-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-pyrrolidine-2-carboxylic acid	559.68
29-54		(R)-1-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-pyrrolidine-2-carboxylic acid	559.68
29-55		3-Cyclopentyl-2-{4-[4-(2-diethylamino-acetyl)-piperazine-1-sulfonyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide	643.85

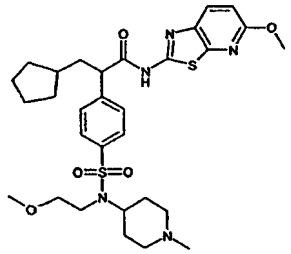
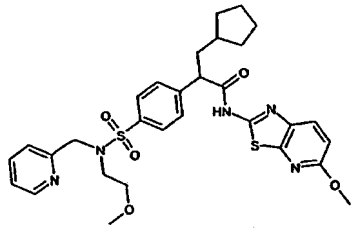
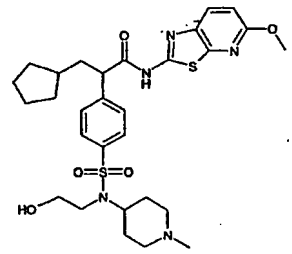
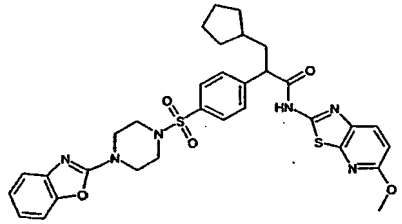
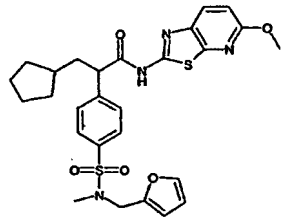
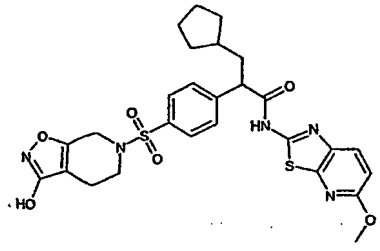
Example	Structure	Chemical name	MS; M+1$^+$
29-56		3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-{4-[(piperidin-3-ylmethyl)-sulfamoyl]-phenyl}-propionamide	558.74
29-57		2-(4-Butyrylsulfamoyl-phenyl)-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide	531.67
29-58		2-[4-(4-Cyanomethyl-piperazine-1-sulfonyl)-phenyl]-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide	569.72
29-59		3-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonylamino}-propionic acid ethyl ester	561.7
29-60		3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-{4-[methyl-(1-methyl-1H-imidazol-2-ylmethyl)-sulfamoyl]-phenyl}-propionamide	569.72
29-61		3-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonylamino}-propionic acid	533.64

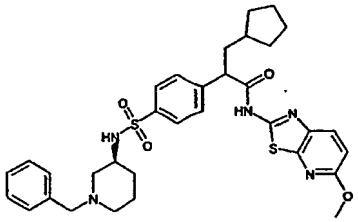
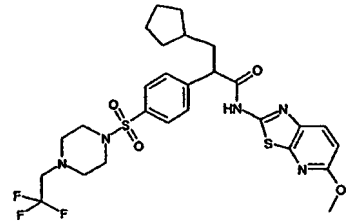
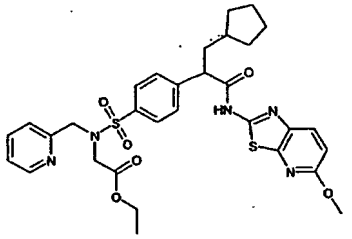
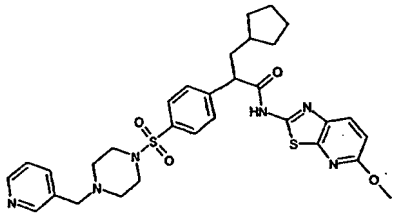
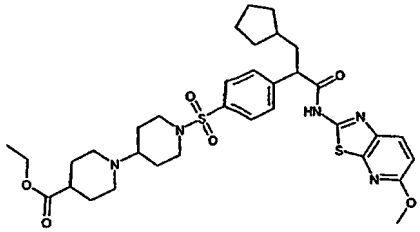
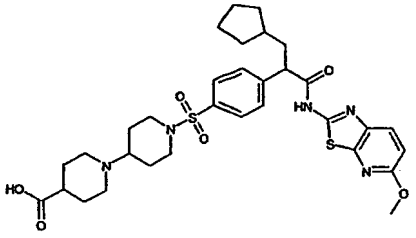
Example	Structure	Chemical name	MS; M+1$^+$
29-62		3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-{4-[3-(4-methyl-piperazin-1-yl)-3-oxo-propylsulfamoyl]-phenyl}-propionamide	615.79
29-63		3-Cyclopentyl-2-{4-[2-(4-hydroxy-piperidin-1-yl)-ethylsulfamoyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide	588.77
29-64		2-[4-(4-Cyclobutyl-piperazine-1-sulfonyl)-phenyl]-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide	584.78
29-65		2-[4-(4-Allyl-piperazine-1-sulfonyl)-phenyl]-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide	570.75
29-66		(1-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-azetidin-3-ylamino)-acetic acid	574.69
29-67		3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(2-piperidin-1-ylmethyl-phenylsulfamoyl)-phenyl]-propionamide	634.84

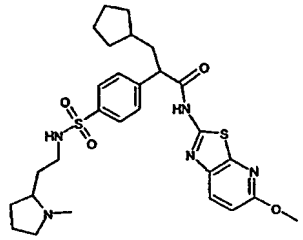
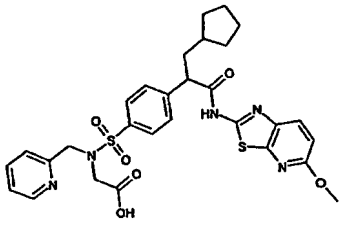
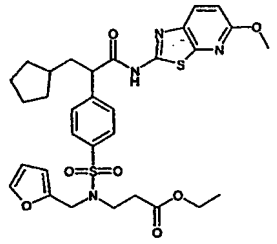
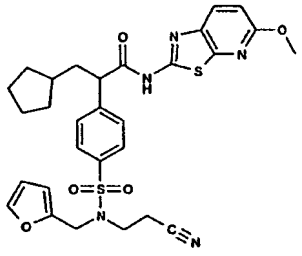
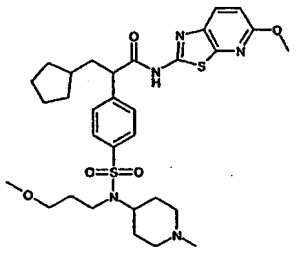
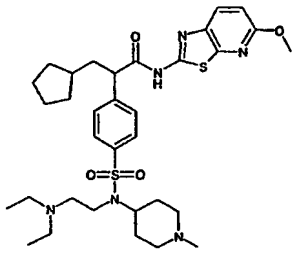
Example	Structure	Chemical name	MS; M+1$^+$
29-68		3-Cyclopentyl-2-{4-[4-(2-dimethylamino-ethyl)-phenylsulfamoyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide	608.8
29-69		3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-(4-propionylsulfamoyl-phenyl)-propionamide	517.64
29-70		[3-({4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonylamino}-methyl)-azetidin-1-yl]-acetic acid	588.72
29-71		3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-{4-[4-(2,2,2-trifluoro-acetyl)-piperazine-1-sulfonyl]-phenyl}-propionamide	626.69
29-72		3-Cyclopentyl-2-[4-(3-isopropylamino-azetidine-1-sulfonyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide	558.74
29-73		3-Cyclopentyl-2-[4-(1-isopropyl-azetidin-3-ylsulfamoyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide	558.74

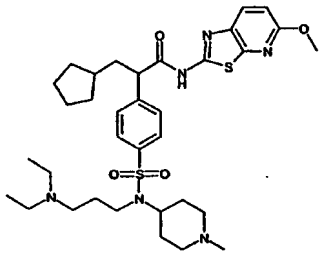
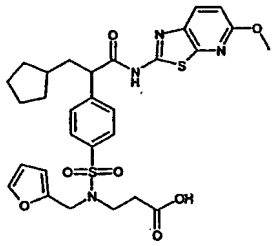
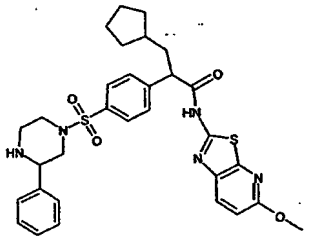
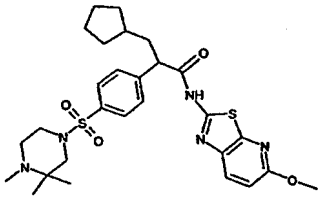
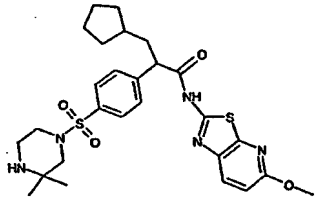
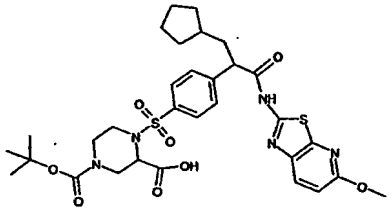
Example	Structure	Chemical name	MS; M+1$^+$
29-74		3-Cyclopentyl-2-{4-[(1-isopropyl-azetidin-3-ylmethyl)-sulfamoyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide	572.77
29-75		3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-{4-[(oxazol-2-ylmethyl)-sulfamoyl]-phenyl}-propionamide	542.65
29-76		3-Cyclopentyl-2-{4-[4-(2-methanesulfonyl-ethyl)-piperazine-1-sulfonyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide	636.83
29-77		2-{4-[4-(3-Cyano-propyl)-piperazine-1-sulfonyl]-phenyl}-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide	597.78
29-78		3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(tetrahydro-pyran-4-ylsulfamoyl)-phenyl]-propionamide	545.7
29-79		3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-{4-[1-(tetrahydro-pyran-4-yl)-azetidin-3-ylsulfamoyl]-phenyl}-propionamide	600.78

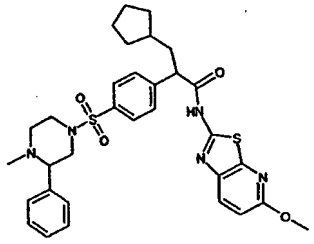
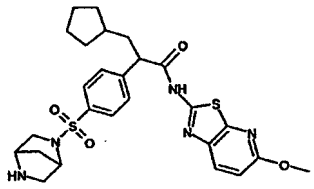
Example	Structure	Chemical name	MS; M+1$^+$
29-80		4-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-3-hydroxymethyl-piperazine-1-carboxylic acid tert-butyl ester	660.83
29-81		(S)-2-tert-Butoxycarbonylamino-4-{4-[2-cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonylamino}-butyric acid tert-butyl ester	718.91
29-82		S)-2-Amino-4-{4-[2-cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonylamino}-butyric acid	562.68
29-83		3-Cyclopentyl-2-{4-[4-(2-imidazol-1-yl-ethyl)-piperazine-1-sulfonyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide	624.8
29-84		3-Cyclopentyl-2-[4-(2-hydroxymethyl-piperazine-1-sulfonyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide	560.71
29-85		(4-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-piperazin-1-yl)-acetic acid	588.72

Example	Structure	Chemical name	MS; M+1$^+$
29-86		3-Cyclopentyl-2-{4-[(2-methoxy-ethyl)-(1-methyl-piperidin-4-yl)-sulfamoyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide	616.82
29-87		3-Cyclopentyl-2-{4-[(2-methoxy-ethyl)-pyridin-2-ylmethyl-sulfamoyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide hydrochloride	610.77
29-88		3-Cyclopentyl-2-{4-[(2-hydroxy-ethyl)-(1-methyl-piperidin-4-yl)-sulfamoyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide	602.79
29-89		2-[4-(4-Benzooxazol-2-yl-piperazine-1-sulfonyl)-phenyl]-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide	647.79
29-90		3-Cyclopentyl-2-[4-(furan-2-ylmethyl-methyl-sulfamoyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide	555.69
29-91		3-Cyclopentyl-2-[4-(3-hydroxy-4,7-dihydro-5H-isoxazolo[5,4-c]pyridine-6-sulfonyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide	584.69

Example	Structure	Chemical name	MS; M+1$^+$
29-92		2-[4-((S)-1-Benzyl-piperidin-3-ylsulfamoyl)-phenyl]-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide	634.84
29-93		3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-{4-[4-(2,2,2-trifluoro-ethyl)-piperazine-1-sulfonyl]-phenyl}-propionamide	612.71
29-94		({4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-pyridin-2-ylmethyl-amino)-acetic acid ethyl ester hydrochloride	638.78
29-95		3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(4-pyridin-3-ylmethyl-piperazine-1-sulfonyl)-phenyl]-propionamide hydrochloride	621.8
29-96		1'-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-[1,4']bipiperidinyl-4-carboxylic acid ethyl ester hydrochloride	684.9
29-97		1'-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-[1,4']bipiperidinyl-4-carboxylic acid hydrochloride	656.84

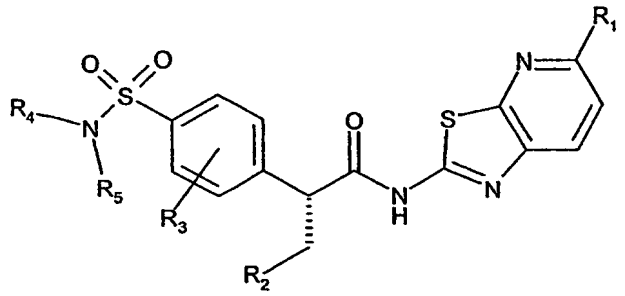
Example	Structure	Chemical name	MS; M+1$^+$
29-98		3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-{4-[2-(1-methyl-pyrrolidin-2-yl)-ethylsulfamoyl]-phenyl}-propionamide	572.77
29-99		({4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-pyridin-2-ylmethyl-amino)-acetic acid	610.73
29-100		3-({4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-furan-2-ylmethyl-amino)-propionic acid ethyl ester	641.78
29-101		2-{4-[(2-Cyano-ethyl)-furan-2-ylmethyl-sulfamoyl]-phenyl}-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide	594.73
29-102		3-Cyclopentyl-2-{4-[(3-methoxy-propyl)-(1-methyl-piperidin-4-yl)-sulfamoyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide	630.85
29-103		3-Cyclopentyl-2-{4-[(2-diethylamino-ethyl)-(1-methyl-piperidin-4-yl)-sulfamoyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide	657.92

Example	Structure	Chemical name	MS; M+1+
29-104		3-Cyclopentyl-2-{4-[(3-diethylamino-propyl)-(1-methyl-piperidin-4-yl)-sulfamoyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide	671.94
29-105		3-({4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-furan-2-ylmethyl-amino)-propionic acid	613.73
29-106		3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(3-phenyl-piperazine-1-sulfonyl)-phenyl]-propionamide	606.78
29-107		3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(3,3,4-trimethyl-piperazine-1-sulfonyl)-phenyl]-propionamide	572.77
29-108		3-Cyclopentyl-2-[4-(3,3-dimethyl-piperazine-1-sulfonyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide	558.74
29-109		4-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-piperazine-1,3-dicarboxylic acid 1-tert-butyl ester	674.81

Example	Structure	Chemical name	MS; M+1$^+$
29-110		3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(4-methyl-3-phenyl-piperazine-1-sulfonyl)-phenyl]-propionamide	620.81
29-111		3-Cyclopentyl-2-[4-(2,5-diaza-bicyclo[2.2.1]heptane-2-sulfonyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide	542.7

What is claimed is:

1. A compound of the formula



(I)

wherein

R_1 is hydrogen, halogen, cyano, nitro, optionally substituted alkyl, alkoxy, alkylthio, alkylthiono, sulfonyl, carboxy, carbamoyl, sulfamoyl or optionally substituted amino;

R_2 is C_3-C_6 cycloalkyl or C_3-C_6 heterocyclyl;

R_3 is hydrogen, halogen, cyano, lower alkyl or lower alkoxy;

R_4 is hydrogen, optionally substituted alkyl, or cycloalkyl;

R_5 is $-(CR_6R_7)_m$-W-R_8 in which

R_6 and R_7 are independently hydrogen, optionally substituted alkyl or cycloalkyl; or

R_6 and R_7 combined are alkylene which together with the carbon atom to which they are attached form a 3- to 7-membered ring;

m is zero or an integer from 1 to 5;

W is $-NR_9-$ in which

R_9 is hydrogen, optionally substituted alkyl or heterocyclyl; or

R_9 is $-C(O)R_{10}$, $-C(O)OR_{10}$, or $-C(O)NR_{10}R_{11}$ in which

R_{10} is optionally substituted alkyl, cycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl;

R_{11} is hydrogen or lower alkyl; or

R_{11} and R_{10} combined are alkylene which together with the nitrogen atom to which they are attached form a 4- to 7-membered ring; or

W is absent;

R_8 is hydrogen, optionally substituted C_1-C_7 alkyl, cycloalkyl, aryl or heterocyclyl; or

R_8 and R_9 combined are alkylene which together with the nitrogen atom to which they are attached form a 4- to 7-membered ring; or

R_5 and R_4 combined are alkylene which together with the nitrogen atom to which they are attached form a 4- to 7-membered ring; or

R_5 and R_4 taken together with the nitrogen atom to which they are attached form a 6- to 12-membered fused, bridged or spiral bicyclic ring, which may be optionally substituted or may contain 1 to 3 other heteroatoms selected from oxygen, nitrogen and sulfur;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

2. A compound according to Claim 1, wherein

R_1 is hydrogen, halogen, cyano, nitro, alkoxy, carboxy, carbamoyl or optionally substituted amino;

R_2 is C_3-C_6 cycloalkyl or C_3-C_6 heterocyclyl;

R_3 is hydrogen, halogen, cyano, lower alkyl or lower alkoxy;

R_4 is hydrogen or lower alkyl;

R_5 is $-(CR_6R_7)_m-W-R_8$ in which

R_6 and R_7 are independently hydrogen or optionally substituted lower alkyl;

m is zero or an integer from 1 to 5;

W is $-NR_9-$ in which

R_9 is hydrogen or lower alkyl; or

R_9 is $-C(O)R_{10}$, $-C(O)OR_{10}$, or $-C(O)NR_{10}R_{11}$ in which

R_{10} is optionally substituted alkyl, cycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl;

R_{11} is hydrogen or lower alkyl; or

R_{11} and R_{10} combined are alkylene which together with the nitrogen atom to which they are attached form a 5- to 7-membered ring; or

W is absent;

R_8 is hydrogen, optionally substituted C_1-C_7 alkyl, cycloalkyl, aryl or heterocyclyl; or

R_8 and R_9 combined are alkylene which together with the nitrogen atom to which they are attached form a 5- to 7-membered ring; or

R_5 and R_4 combined are alkylene which together with the nitrogen atom to which they are attached form a 5- to 7-membered ring;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

3. A compound according to Claim 2, wherein

R_4 is hydrogen or lower alkyl;

R_5 is $-(CR_6R_7)_m-W-R_8$ in which

R_6 and R_7 are independently hydrogen or optionally substituted lower alkyl;

m is an integer from 2 to 5;

W is $-NR_9-$ in which

R_9 is hydrogen or lower alkyl; or

R_9 is $-C(O)R_{10}$, $-C(O)OR_{10}$, or $-C(O)NR_{10}R_{11}$ in which

R_{10} is optionally substituted alkyl, cycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl;

R_{11} is hydrogen or lower alkyl; or

R_{11} and R_{10} combined are alkylene which together with the nitrogen atom to which they are attached form a 5- to 7-membered ring; or

R_8 is hydrogen, optionally substituted C_1-C_7 alkyl, cycloalkyl, aryl or heterocyclyl; or

R_8 and R_9 combined are alkylene which together with the nitrogen atom to which they are attached form a 5- to 7-membered ring;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

4. A compound according to Claim 3, wherein

R_1 is hydrogen, halogen, C_1-C_4 alkoxy, carboxy or carbamoyl;

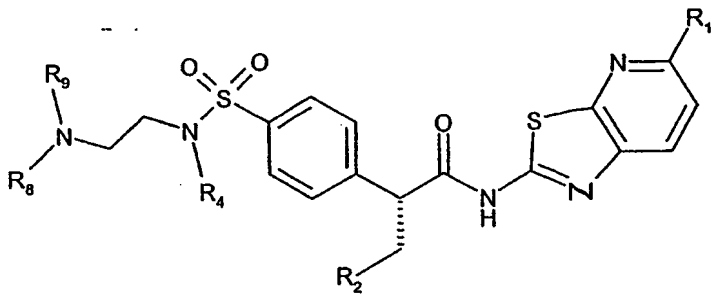
R_2 is C_3-C_5 cycloalkyl;

R_3 is hydrogen;

R_6 and R_7 are hydrogen;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

5. A compound according to Claim 4 of the formula



(IA)

wherein

R_1 is hydrogen, halogen, C_1-C_4 alkoxy, carboxy or carbamoyl;

R_2 is C_3-C_5 cycloalkyl;

R_4 is hydrogen or lower alkyl;

R_8 is hydrogen, optionally substituted C_1-C_7 alkyl, cycloalkyl, aryl or heterocyclyl;

R_9 is hydrogen or lower alkyl; or

R_9 is $-C(O)R_{10}$, $-C(O)OR_{10}$, or $-C(O)NR_{10}R_{11}$ in which

R_{10} is optionally substituted alkyl, cycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl;

R_{11} is hydrogen or lower alkyl; or

R_{11} and R_{10} combined are alkylene which together with the nitrogen atom to which they are attached form a 5- to 7-membered ring; or

R_9 and R_8 combined are alkylene which together with the nitrogen atom to which they are attached form a 5- to 7-membered ring;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

6. A compound according to Claim 5, wherein

R_1 is methoxy;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

7. A compound according to Claim 5, wherein

R_2 is cyclopentyl;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

8. A compound according to Claim 5, wherein

R_1 is methoxy;

R_2 is cyclopentyl;

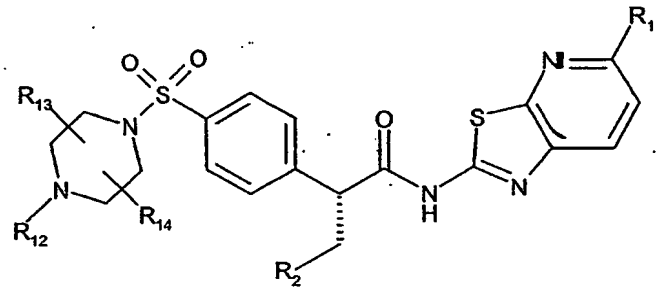
or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

9. A compound according to Claim 1, wherein

R_4 and R_5 combined are alkylene which together with the nitrogen atom to which they are attached form a 5- to 7-membered ring;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

10. A compound according to Claim 9 of the formula



(IB)

wherein

R_1 is hydrogen, halogen, C_1-C_4 alkoxy, carboxy or carbamoyl;

R_2 is C_3-C_5 cycloalkyl;

R_{12} is hydrogen, optionally substituted lower alkyl, cycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl; or

R_{12} is $-C(O)R_{15}$, $-C(O)OR_{15}$, or $-C(O)NR_{15}R_{16}$ in which

R_{15} optionally substituted alkyl, cycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl;

R_{16} is hydrogen or lower alkyl; or

R_{16} and R_{15} combined are alkylene which together with the nitrogen atom to which they are attached form a 5- to 7-membered ring;

R_{13} and R_{14} are independently hydrogen or lower alkyl;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

11. A compound according to Claim 10, wherein

R_1 is methoxy;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

12. A compound according to Claim 10, wherein

R_2 is cyclopentyl;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

13. A compound according to Claim 10, wherein

R_1 is methoxy;

R_2 is cyclopentyl;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

14. A compound according to Claim 10, wherein

R_{12} is methyl;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

15. A compound according to Claim 10, wherein

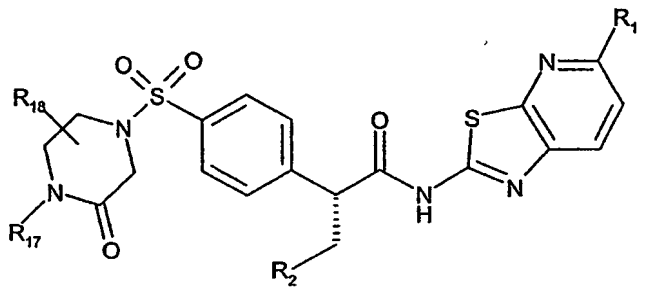
R_1 is methoxy;

R_2 is cyclopentyl;

R_{13} and R_{14} are independently hydrogen or methyl;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

16. A compound according to Claim 9 of the formula



(IC)

wherein

R_1 is hydrogen, halogen, C_1-C_4 alkoxy, carboxy or carbamoyl;

R_2 is C_3-C_5 cycloalkyl;

R_{17} is hydrogen, optionally substituted lower alkyl, cycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl;

R_{18} is hydrogen or lower alkyl;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

17. A compound according to Claim 16, wherein

R_1 is methoxy;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

18. A compound according to Claim 16, wherein

R_2 is cyclopentyl;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

19. A compound according to Claim 16, wherein

R_1 is methoxy;

R_2 is cyclopentyl;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

20. A compound according to Claim 16, wherein

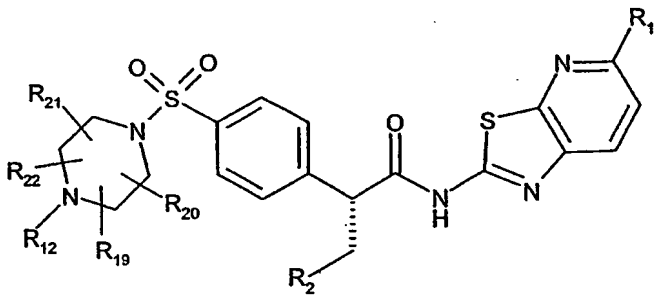
R_1 is methoxy;

R_2 is cyclopentyl;

R_{18} is hydrogen or methyl;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

21. A compound according to Claim 9 of the formula



(ID)

wherein

R_1 is hydrogen, halogen, C_1-C_4 alkoxy, carboxy or carbamoyl;

R_2 is C_3-C_5 cycloalkyl;

R_{12} is hydrogen, optionally substituted lower alkyl, cycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl; or

R_{12} is -C(O)R_{15}, -C(O)OR_{15}, or -C(O)N$R_{15}R_{16}$ in which

R_{15} optionally substituted alkyl, cycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl;

R_{16} is hydrogen or lower alkyl; or

R_{16} and R_{15} combined are alkylene which together with the nitrogen atom to which they are attached form a 5- to 7-membered ring;

R_{19}, R_{20}, R_{21} and R_{22} are independently hydrogen, optionally substituted lower alkyl, cycloalkyl, aryl or heterocyclyl;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

22. A compound according to Claim 21, wherein

R_1 is methoxy;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

23. A compound according to Claim 21, wherein

R_2 is cyclopentyl;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

24. A compound according to Claim 21, wherein

R_1 is methoxy;

R_2 is cyclopentyl;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

25. A compound according to Claim 21, wherein

R_{12} is methyl;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

26. A compound according to Claim 21, wherein

R_1 is methoxy;

R_2 is cyclopentyl;

R_{19}, R_{20}, R_{21} and R_{22} are methyl;

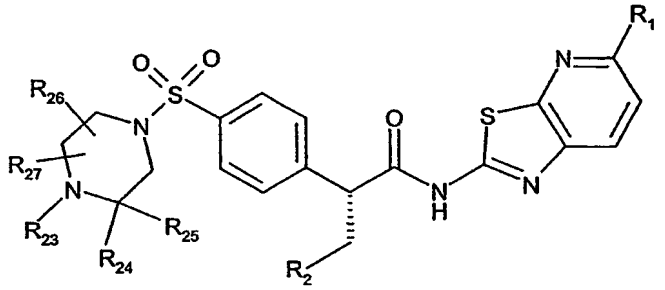
or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

27. A compound according to Claim 1, wherein

R_4 and R_5 taken together with the nitrogen atom to which they are attached form a 8- to 12-membered fused, bridged or spiral bicyclic ring, which may be optionally substituted or may contain 1 to 3 other heteroatoms selected from oxygen, nitrogen and sulfur;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

28. A compound according to Claim 27 of the formula



(IE)

wherein

R_1 is hydrogen, halogen, C_1-C_4 alkoxy, carboxy or carbamoyl;

R_2 is C_3-C_5 cycloalkyl;

R_{12} is hydrogen, optionally substituted lower alkyl, cycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl; or

R_{23} is $-C(O)R_{15}$, $-C(O)OR_{15}$, or $-C(O)NR_{15}R_{16}$ in which

R_{15} optionally substituted alkyl, cycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl;

R_{16} is hydrogen or lower alkyl; or

R_{16} and R_{15} combined are alkylene which together with the nitrogen atom to which they are attached form a 5- to 7-membered ring; or

R_{23} and R_{24} combined are alkylene which together with the nitrogen and carbon atoms to which they are attached form a 4- to 7-membered ring;

R_{25} is hydrogen; or

R_{25} and R_{24} combined are alkylene which together with the carbon atom to which they are attached form a 3- to 7-membered ring;

R_{26} and R_{27} are independently optionally substituted lower alkyl, cycloalkyl, aryl or heterocyclyl;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

29. A compound according to Claim 28, wherein

R_1 is methoxy;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

30. A compound according to Claim 28, wherein

R_2 is cyclopentyl;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

31. A compound according to Claim 28, wherein

R_1 is methoxy;

R_2 is cyclopentyl;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

32. A compound according to Claim 1 which is selected from:

3-Cyclopentyl-2-(4-cyclopropylsulfamoyl-phenyl)-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;
3-Cyclopentyl-2-[4-(2-methoxy-ethylsulfamoyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;
3-Cyclopentyl-2-[4-(3-methoxy-benzylsulfamoyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;
3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-(4-phenylsulfamoyl-phenyl)-propionamide;
2-[4-(2-Carbamoyl-ethylsulfamoyl)-phenyl]-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;
3-Cyclopentyl-2-(4-diisopropylsulfamoyl-phenyl)-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;
3-Cyclopentyl-2-{4-[(furan-2-ylmethyl)-sulfamoyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;
3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(phenyl-propyl-sulfamoyl)-phenyl]-propionamide;
3-Cyclopentyl-2-(4-dimethylsulfamoyl-phenyl)-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;
3-Cyclopentyl-2-(4-diethylsulfamoyl-phenyl)-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;
3-Cyclopentyl-2-(4-dipropylsulfamoyl-phenyl)-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;
3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-{4-[(pyridin-3-ylmethyl)-sulfamoyl]-phenyl}-propionamide;
2-(4-Cyclohexylsulfamoyl-phenyl)-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;
3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(piperidine-1-sulfonyl)-phenyl]-propionamide;
3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(morpholine-4-sulfonyl)-phenyl]-propionamide;
3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-{4-[(thiophen-2-ylmethyl)-sulfamoyl]-phenyl}-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(pyridin-3-ylsulfamoyl)-phenyl]-propionamide;

3-Cyclopentyl-2-[4-(2-fluoro-benzylsulfamoyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-2-[4-(4-methoxy-benzylsulfamoyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

2-(4-Benzylsulfamoyl-phenyl)-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

2-[4-(Benzyl-methyl-sulfamoyl)-phenyl]-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(4-methyl-piperazine-1-sulfonyl)-phenyl]-propionamide;

3-Cyclopentyl-2-(4-dibutylsulfamoyl-phenyl)-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-2-[4-(4-ethyl-piperazine-1-sulfonyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

2-[4-(4-Acetyl-piperazine-1-sulfonyl)-phenyl]-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(piperazine-1-sulfonyl)-phenyl]-propionamide hydrochloride;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(4-phenyl-piperazine-1-sulfonyl)-phenyl]-propionamide;

3-Cyclopentyl-2-{4-[4-(2-methoxy-phenyl)-piperazine-1-sulfonyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

2-{4-[4-(3-Chloro-phenyl)-piperazine-1-sulfonyl]-phenyl}-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

2-[4-(4-Benzyl-piperazine-1-sulfonyl)-phenyl]-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-2-[4-(4-isopropyl-piperazine-1-sulfonyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(4-o-tolyl-piperazine-1-sulfonyl)-phenyl]-propionamide;

N-[2-(2-{4-[4-(2-Chloro-phenyl)-piperazine-1-sulfonyl]-phenyl}-3-cyclopentyl-propionylamino)-thiazol-5-yl]-acetimidic acid methyl ester;

3-Cyclopentyl-2-{4-[4-(4-fluoro-phenyl)-piperazine-1-sulfonyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(4-pyridin-2-yl-piperazine-1-sulfonyl)-phenyl]-propionamide;

3-Cyclopentyl-2-{4-[(2-hydroxy-ethyl)-methyl-sulfamoyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(4-pyridin-4-yl-piperazine-1-sulfonyl)-phenyl]-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(2-piperidin-1-yl-ethylsulfamoyl)-phenyl]-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(2-pyrrolidin-1-yl-ethylsulfamoyl)-phenyl]-propionamide;

3-Cyclopentyl-2-{4-[(2-dimethylamino-ethyl)-ethyl-sulfamoyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide hydrochloride;

3-Cyclopentyl-2-[4-(2-dimethylamino-ethylsulfamoyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide hydrochloride;

3-Cyclopentyl-2-{4-[4-(2-hydroxy-ethyl)-piperazine-1-sulfonyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-{4-[methyl-(2-pyrrolidin-1-yl-ethyl)-sulfamoyl]-phenyl}-propionamide hydrochloride;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-{4-[methyl-(2-piperidin-1-yl-ethyl)-sulfamoyl]-phenyl}-propionamide hydrochloride;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-{4-[methyl-(2-morpholin-4-yl-ethyl)-sulfamoyl]-phenyl}-propionamide;

4-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-piperazin-1-yl)-acetic acid ethyl ester;

3-Cyclopentyl-2-{4-[(2-diethylamino-ethyl)-methyl-sulfamoyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-2-[4-(2-hydroxy-ethylsulfamoyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

2-[4-(4-Carbamoylmethyl-piperazine-1-sulfonyl)-phenyl]-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(pyrrolidine-1-sulfonyl)-phenyl]-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(pyridin-2-ylsulfamoyl)-phenyl]-propionamide;

4-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonylamino}-piperidine-1-carboxylic acid tert-butyl ester;

4-({4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonylamino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester;

3-Cyclopentyl-2-{4-[(1-ethyl-pyrrolidin-2-ylmethyl)-sulfamoyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(piperidin-4-ylsulfamoyl)-phenyl]-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-{4-[(piperidin-4-ylmethyl)-sulfamoyl]-phenyl}-propionamide;

(4-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-piperazin-1-yl)-acetic acid ethyl ester;

3-Cyclopentyl-2-{4-[(3-hydroxy-5-hydroxymethyl-2-methyl-pyridin-4-ylmethyl)-sulfamoyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonylamino}-azetidine-1-carboxylic acid tert-butyl ester;

(1-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-azetidin-3-yl)-carbamic acid tert-butyl ester;

3-({4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonylamino}-methyl)-azetidine-1-carboxylic acid tert-butyl ester;

1-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-pyrrolidine-2-carboxylic acid;

2-[4-(Azetidin-3-ylsulfamoyl)-phenyl]-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

2-[4-(3-Amino-azetidine-1-sulfonyl)-phenyl]-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

2-{4-[(Azetidin-3-ylmethyl)-sulfamoyl]-phenyl}-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-(4-sulfamoyl-phenyl)-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-{4-[(pyridin-4-ylmethyl)-sulfamoyl]-phenyl}-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-{4-[(pyridin-2-ylmethyl)-sulfamoyl]-phenyl}-propionamide;

4-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonylamino}-benzoic acid;

3-Cyclopentyl-2-[4-(4-dimethylamino-phenylsulfamoyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

2-[4-(4-Cyclohexylmethyl-piperazine-1-sulfonyl)-phenyl]-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(1,2,2,6,6-pentamethyl-piperidin-4-ylsulfamoyl)-phenyl]-propionamide;

3-Cyclopentyl-2-[4-(1,1-dimethyl-2-morpholin-4-yl-ethylsulfamoyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

(S)-3-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonylamino}-piperidine-1-carboxylic acid tert-butyl ester;

2-[4-([1,4']Bipiperidinyl-1'-sulfonyl)-phenyl]-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-2-[4-(4-diethylamino-piperidine-1-sulfonyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(4-pyrrolidin-1-yl-piperidine-1-sulfonyl)-phenyl]-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(octahydro-pyrido[1,2-a]pyrazine-2-sulfonyl)-phenyl]-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(pyridin-4-ylsulfamoyl)-phenyl]-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-((S)-piperidin-3-ylsulfamoyl)-phenyl]-propionamide;

3-Cyclopentyl-2-[4-(1-ethyl-piperidin-3-ylsulfamoyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

2-{4-[4-(2-Cyano-ethyl)-piperazine-1-sulfonyl]-phenyl}-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(4-piperidin-1-ylmethyl-phenylsulfamoyl)-phenyl]-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(1-phenyl-2-pyrrolidin-1-yl-ethylsulfamoyl)-phenyl]-propionamide;

2-[4-(4-Cyclohexyl-piperazine-1-sulfonyl)-phenyl]-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-2-[4-(2-dimethylamino-2-pyridin-3-yl-ethylsulfamoyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-{4-[methyl-(1-methyl-piperidin-4-yl)-sulfamoyl]-phenyl}-propionamide;

2-[4-(4-Cyclooctyl-piperazine-1-sulfonyl)-phenyl]-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(4-phenethyl-piperazine-1-sulfonyl)-phenyl]-propionamide;

(R)-3-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonylamino}-piperidine-1-carboxylic acid tert-butyl ester;

3-Cyclopentyl-2-{4-[4-(2-ethoxy-ethyl)-piperazine-1-sulfonyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-2-{4-[4-(2-diethylamino-ethyl)-piperazine-1-sulfonyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-((R)-piperidin-3-ylsulfamoyl)-phenyl]-propionamide;

(1-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-azetidin-3-ylamino)-acetic acid ethyl ester;

[3-({4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonylamino}-methyl)-azetidin-1-yl]-acetic acid ethyl ester;

3-Cyclopentyl-2-[4-(hexahydro-pyrrolo[1,2-a]pyrazine-2-sulfonyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

4-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonylamino}-piperidine-1-carboxylic acid ethyl ester;

3-Cyclopentyl-2-{4-[cyclopropyl-(1-methyl-piperidin-4-yl)-sulfamoyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

2-[4-(4-Benzyl-4,7-diaza-spiro[2.5]octane-7-sulfonyl)-phenyl]-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-{4-[4-(4-methyl-piperazin-1-yl)-piperidine-1-sulfonyl]-phenyl}-propionamide;

3-Cyclopentyl-2-[4-(4-cyclopentyl-piperazine-1-sulfonyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-2-[4-(4,7-diaza-spiro[2.5]octane-7-sulfonyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-({4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonylamino}-methyl)-piperidine-1-carboxylic acid tert-butyl ester;

(S)-1-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-pyrrolidine-2-carboxylic acid;

(R)-1-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-pyrrolidine-2-carboxylic acid;

3-Cyclopentyl-2-{4-[4-(2-diethylamino-acetyl)-piperazine-1-sulfonyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-{4-[(piperidin-3-ylmethyl)-sulfamoyl]-phenyl}-propionamide;

2-(4-Butyrylsulfamoyl-phenyl)-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

2-[4-(4-Cyanomethyl-piperazine-1-sulfonyl)-phenyl]-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonylamino}-propionic acid ethyl ester;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-{4-[methyl-(1-methyl-1H-imidazol-2-ylmethyl)-sulfamoyl]-phenyl}-propionamide;

3-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonylamino}-propionic acid;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-{4-[3-(4-methyl-piperazin-1-yl)-3-oxo-propylsulfamoyl]-phenyl}-propionamide;

3-Cyclopentyl-2-{4-[2-(4-hydroxy-piperidin-1-yl)-ethylsulfamoyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)–propionamide;

2-[4-(4-Cyclobutyl-piperazine-1-sulfonyl)-phenyl]-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

2-[4-(4-Allyl-piperazine-1-sulfonyl)-phenyl]-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

(1-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-azetidin-3-ylamino)-acetic acid;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(2-piperidin-1-ylmethyl-phenylsulfamoyl)-phenyl]-propionamide;

3-Cyclopentyl-2-{4-[4-(2-dimethylamino-ethyl)-phenylsulfamoyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)–propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-(4-propionylsulfamoyl-phenyl)-propionamide;

[3-({4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonylamino}-methyl)-azetidin-1-yl]-acetic acid;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-{4-[4-(2,2,2-trifluoro-acetyl)-piperazine-1-sulfonyl]-phenyl}-propionamide;

3-Cyclopentyl-2-[4-(3-isopropylamino-azetidine-1-sulfonyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-2-[4-(1-isopropyl-azetidin-3-ylsulfamoyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-2-{4-[(1-isopropyl-azetidin-3-ylmethyl)-sulfamoyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-{4-[(oxazol-2-ylmethyl)-sulfamoyl]-phenyl}-propionamide;

3-Cyclopentyl-2-{4-[4-(2-methanesulfonyl-ethyl)-piperazine-1-sulfonyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

2-{4-[4-(3-Cyano-propyl)-piperazine-1-sulfonyl]-phenyl}-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(tetrahydro-pyran-4-ylsulfamoyl)-phenyl]-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-{4-[1-(tetrahydro-pyran-4-yl)-azetidin-3-ylsulfamoyl]-phenyl}-propionamide;

4-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-3-hydroxymethyl-piperazine-1-carboxylic acid tert-butyl ester;

(S)-2-tert-Butoxycarbonylamino-4-{4-[2-cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonylamino}-butyric acid tert-butyl ester;

S)-2-Amino-4-{4-[2-cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonylamino}-butyric acid;

3-Cyclopentyl-2-{4-[4-(2-imidazol-1-yl-ethyl)-piperazine-1-sulfonyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-2-[4-(2-hydroxymethyl-piperazine-1-sulfonyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

(4-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-piperazin-1-yl)-acetic acid;

3-Cyclopentyl-2-{4-[(2-methoxy-ethyl)-(1-methyl-piperidin-4-yl)-sulfamoyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-2-{4-[(2-methoxy-ethyl)-pyridin-2-ylmethyl-sulfamoyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide hydrochloride;

3-Cyclopentyl-2-{4-[(2-hydroxy-ethyl)-(1-methyl-piperidin-4-yl)-sulfamoyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

2-[4-(4-Benzooxazol-2-yl-piperazine-1-sulfonyl)-phenyl]-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-2-[4-(furan-2-ylmethyl-methyl-sulfamoyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-2-[4-(3-hydroxy-4,7-dihydro-5H-isoxazolo[5,4-c]pyridine-6-sulfonyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

2-[4-((S)-1-Benzyl-piperidin-3-ylsulfamoyl)-phenyl]-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-{4-[4-(2,2,2-trifluoro-ethyl)-piperazine-1-sulfonyl]-phenyl}-propionamide;

({4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-pyridin-2-ylmethyl-amino)-acetic acid ethyl ester hydrochloride;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(4-pyridin-3-ylmethyl-piperazine-1-sulfonyl)-phenyl]-propionamide hydrochloride;

1'-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-[1,4']bipiperidinyl-4-carboxylic acid ethyl ester hydrochloride;

1'-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-[1,4']bipiperidinyl-4-carboxylic acid hydrochloride;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-{4-[2-(1-methyl-pyrrolidin-2-yl)-ethylsulfamoyl]-phenyl}-propionamide;

({4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-pyridin-2-ylmethyl-amino)-acetic acid;

3-({4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-furan-2-ylmethyl-amino)-propionic acid ethyl ester;

2-{4-[(2-Cyano-ethyl)-furan-2-ylmethyl-sulfamoyl]-phenyl}-3-cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-2-{4-[(3-methoxy-propyl)-(1-methyl-piperidin-4-yl)-sulfamoyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-2-{4-[(2-diethylamino-ethyl)-(1-methyl-piperidin-4-yl)-sulfamoyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-Cyclopentyl-2-{4-[(3-diethylamino-propyl)-(1-methyl-piperidin-4-yl)-sulfamoyl]-phenyl}-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

3-({4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-furan-2-ylmethyl-amino)-propionic acid;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(3-phenyl-piperazine-1-sulfonyl)-phenyl]-propionamide;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(3,3,4-trimethyl-piperazine-1-sulfonyl)-phenyl]-propionamide;

3-Cyclopentyl-2-[4-(3,3-dimethyl-piperazine-1-sulfonyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

4-{4-[2-Cyclopentyl-1-(5-methoxy-thiazolo[5,4-b]pyridin-2-ylcarbamoyl)-ethyl]-benzenesulfonyl}-piperazine-1,3-dicarboxylic acid 1-tert-butyl ester;

3-Cyclopentyl-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-2-[4-(4-methyl-3-phenyl-piperazine-1-sulfonyl)-phenyl]-propionamide; and

3-Cyclopentyl-2-[4-(2,5-diaza-bicyclo[2.2.1]heptane-2-sulfonyl)-phenyl]-N-(5-methoxy-thiazolo[5,4-b]pyridin-2-yl)-propionamide;

or an enantiomer thereof; or an enantiomeric mixture thereof; or a pharmaceutically acceptable salt thereof.

33. A method for the activation of glucokinase activity in mammals which method comprises administering to a mammal in need thereof a therapeutically effective amount of a compound of Claim 1.

34. A method for the treatment of conditions associated with glucokinase activity in mammals which method comprises administering to a mammal in need thereof a therapeutically effective amount of a compound of Claim 1.

35. A method according to Claim 34, which method comprises administering said compound in combination with a therapeutically effective amount of an anti-diabetic agents, a hypolipidemic agent, an anti-obesity agent or an anti-hypertensive agent.

36. A method for the treatment of impaired glucose tolerance, Type 2 diabetes and obesity which method comprises administering to a mammal in need thereof a therapeutically effective amount of a compound of Claim 1.

37. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 1 in combination with one or more pharmaceutically acceptable carriers.

38. A pharmaceutical composition according to Claim 37 for the treatment of impaired glucose tolerance, Type 2 diabetes and obesity.

39. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 1 in combination with a therapeutically effective amount of an anti-diabetic agents, a hypolipidemic agent, an anti-obesity agent or an anti-hypertensive agent.

40. A pharmaceutical composition according to Claim 39 for the treatment of impaired glucose tolerance, Type 2 diabetes and obesity.

41. A pharmaceutical composition according to Claim 37 or 39, for use as medicament.

42. Use of a pharmaceutical composition according to Claim 37 or 39, for the preparation of a medicament for the treatment of conditions associated with glucokinase activity.

43. Use of a compound according to Claim 1, for the preparation of a pharmaceutical composition for the treatment of conditions associated with glucokinase activity.

44. Use according to claim 42 or 43, wherein the condition associated with glucokinase activity is selected from impaired glucose tolerance, Type 2 diabetes and obesity.

45. A compound according to Claim 1, for use as a medicament.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2005/003456

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D513/04 A61K31/429

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 03/080585 A (BANYU PHARMACEUTICAL CO., LTD; NISHIMURA, TERUYUKI; IINO, TOMOHARU; NA) 2 October 2003 (2003-10-02) abstract page 85; compound 84	1-45
A	WO 02/46173 A (F. HOFFMANN-LA ROCHE AG) 13 June 2002 (2002-06-13) claim 1	1-45
P,X	WO 2004/050645 A (NOVARTIS AG; NOVARTIS PHARMA GMBH; BEBERNITZ, GREGORY, RAYMOND) 17 June 2004 (2004-06-17) claim 6	1-45

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 June 2005	22/07/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Samsam Bakhtiary, M

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2005/003456

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03080585 A	02-10-2003	AU 2003221140 A1	08-10-2003
		CA 2488161 A1	02-10-2003
		EP 1496052 A1	12-01-2005
		WO 03080585 A1	02-10-2003
WO 0246173 A	13-06-2002	AU 2190202 A	18-06-2002
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		CN 1476438 A	18-02-2004
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		WO 2004050645 A1	17-06-2004

Specification

Substituted quinazoline or pyridopyrimidine derivative.

The Field of Technology

This invention relates to the following, namely, substituted quinazoline or pyridopyrimidine derivative.

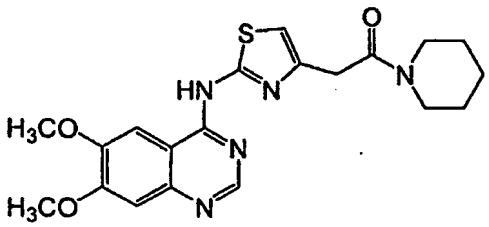
Background Technique

Glucokinase (GK)-(ATP: D-hexose 6-phosphotransferaze, EC2.7.1.1) is one of four kinds of hexokinases of mammals (hexokinase IV). Hexokinase is the enzyme of the first step of the glycolytic pathway, and catalyses reaction of glucose to glucose 6 phosphate.

Expression of glucokinase is localized mainly in liver and pancreatic β cell, and by controlling rate-limiting step of glucose metabolism in these cells, glucokinase performs an important role in glucose metabolism of whole body. The 15 amino acids at the N end of glucokinases of liver and pancreatic β cell have a different sequence, due to a difference of splicing. However, enzyme characteristic is same. Km with respect to glucose of glucokinase is near to the physiological blood glucose level of 8 mM, whereas the enzyme activity of the other three hexokinases excluding glucokinase (I, II, III) is saturated with glucose concentration 1 mM or less.

Accordingly glucokinase causes facilitation of intracellular glucose metabolism by responding to blood glucose change of postprandial blood glucose rise (10-15 mM) from normal blood sugar level (5 mM).

As compound with structure related to compound in accordance with this invention, compound represented by formula (A)

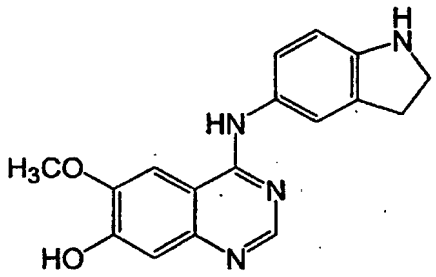


(A)

is described (cf; for example Tokyuho 2004-501914).

However, the compound represented by the aforesaid formulae (A) has methoxy group in around 7 of quinazoline skeleton, and in contrast to this, the compound in accordance with this invention differs in having hydrogen atom or fluorine atom at that point. Moreover, there is not concrete description of compound where there is hydrogen or fluorine atom at 7 position of quinazoline skeleton.

Moreover, as compound reported as targeting diabetes mellitus disease and having quinazoline skeleton, for example,the compound represented by formula (B)



(B)

is described (cf. for example Tokuhyo 2002-536414). The compound represented by the aforesaid formula (B) has quinazoline skeleton, and has methoxy group at 6-position of quinazoline ring, in common with compound in accordance with this invention. However, compound represented by formula (B) has hydroxy group at 7 position of quinazoline ring, and group bonded to the amino group bonded to 4 position of quinazoline ring, which is different in compound in accordance with this invention.

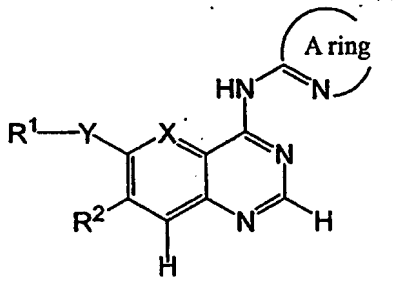
Disclosure of the Invention

This invention has the object of putting forward novel substance having glucokinase activation action.

These inventors discovered that specific substituted quinazoline or pyridopyrimidine derivative had glucokinase activation action. This invention was completed as a result of this discovery.

In other words, this invention puts forward compound in accordance with following (a)-(i) or pharmacologically acceptable salts thereof in order to achieve the aforesaid object.

(a). A compound represented by formula (I) or the pharmacologically acceptable salts thereof



(I)

[wherein, X denotes a nitrogen atom or CH, Y denotes an oxygen atom or sulfur atom, and R^1 denotes an atom or a group arbitrarily selected from the following (1), (2), (3), (4), (5) and (6) (wherein, when R^1 is the following (1) to (5), is, and R^1 may contain the same or different 1-3 groups selected from the substituent group α),

(1) 5-6 membered heteroaryl group containing 1-3 heteroatoms selected from the group comprising a nitrogen atom, sulfur atom and oxygen atom in ring (said heteroaryl group may form a condensed ring with phenyl group),

(2) aryl group,

(3) straight or branched chain lower alkyl group,

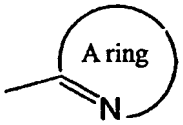
(4) 3-7C cycloalkyl group (one of carbon atom constituting the said group (except carbon atom bonding to Y) may be substituted by oxygen atom, NH, N-alkanoyl group or carbonyl oxy group),

(5) straight or branched chain lower alkenyl group,

(6) hydrogen atom

R^2 denotes a hydrogen atom or fluorine atom,

A ring is a monocyclic or bicyclic heteroaryl group represented by formula (II)



(II)

(the said heteroaryl group may contain one (sic, it must be one or more or one to some specific number) the same or different substituents selected from substituent group β)].

Substituent group α: lower alkyl group (the said lower alkyl group may be substituted 1-3 by halogen atom), 3-7C cycloalkyl group, lower alkoxy group, hydroxy group, hydroxyalkyl group (hydrogen atom of hydroxy group in said hydroxyalkyl group may be substituted by lower alkyl group), alkanoyl group, halogen atom, oxo group, lower alkyl sulphonyl group, lower alkyl sulfonyl amino group, mono- or di-lower alkylcarbamoyl group, mono- or di-lower alkylcarbamoyl alkyl group, mono- or di-lower alkyl sulphamoyl group, amino group, mono- or di-lower alkylamino group, cyano group, and 5-6 membered heteroaryl group which may contain 1-3 heteroatoms selected from the group comprising nitrogen atom, sulfur atom and oxygen atom in ring.

Substituent group β: lower alkyl group, lower alkoxy group, halogen atom, trifluoromethyl group, hydroxyalkyl group (hydrogen atom of hydroxy group in said hydroxyalkyl group may be further substituted by lower alkyl group), amino alkyl group (amino group in said amino alkyl group may be further substituted by lower alkyl group), alkanoyl group, carboxyl group, alkoxycarbonyl group and cyano group.

(b). A compound or pharmacologically acceptable salts thereof in accordance with (a), wherein R^1 is a group arbitrarily selected from the following (1), (2), (3) and (4) (wherein the said R^1 may contain the same or different 1-3 groups selected from the aforesaid substituent group α).

(1) 5-6 membered heteroaryl group containing 1-3 heteroatoms selected from the group comprising nitrogen atom, sulfur atom and oxygen atom in ring (the said heteroaryl group may form a condensed ring with phenyl group),

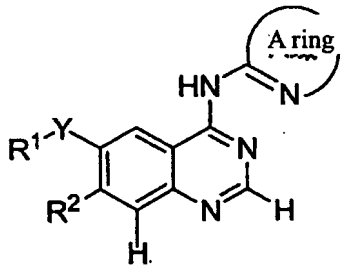
(2) aryl group,

(3) straight or branched chain lower alkyl group,
(4) 1 or 2 of 3-7C cycloalkyl group (carbon atom constituting the said group (except carbon atom bonding to Y) may be substituted by oxygen atom, nitrogen, N-alkanoyl group or carbonyl oxy group, and moreover, 1 or 2 double bonds may be contain in ring).

(c). A compound or pharmacologically acceptable salts thereof in accordance with (a), wherein R^1 is a group arbitrarily selected from the following (1) and (2) (wherein the said R^1 may contain the same or different 1-3 groups selected from the aforesaid substituent group α),.
(1) 5-6 membered heteroaryl group containing 1-3 heteroatoms selected from the group comprising nitrogen atom, sulfur atom and oxygen atom in ring (the said heteroaryl group may form a condensed ring with phenyl group),
(2) aryl group.

(d). A compound or pharmacologically acceptable salts thereof in accordance with (c), wherein A ring is a thiazolo [5,4-b] pyridinyl group, pyrazinyl group, thiadiazolyl group or pyrazolyl group which may contain the same or different 1-3 substituents selected from the substituent group β.

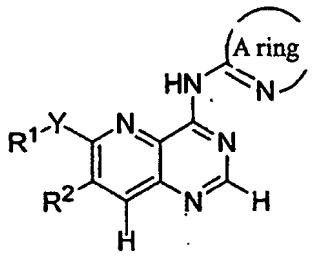
(e). A compound or pharmacologically acceptable salts thereof in accordance with either of (c) or (d), wherein formula (I) is formula (I-1)



(I-1)

(wherein each symbol is the same as above).

(f). A compound or pharmacologically acceptable salts thereof in accordance with either of (c) or (d), wherein formula (I) is formula (I-2)



(I-2)

(wherein each symbol is the same as above).

(g). A compound or pharmacologically acceptable salts thereof in accordance with (e), wherein Y is an oxygen atom.

(h). A compound or pharmacologically acceptable salts thereof in accordance with (f), wherein Y is a sulfur atom,.

(i). A compound or pharmacologically acceptable salts thereof in accordance with (a), wherein the compound represented by formula (I) is
[6-(4H-[1,2,4] triazol-3-yl sulphanyl]-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,
[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-thiazol-2-yl-amine,
[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-pyrazin-2-yl-amine,
(6-phenoxy quinazolin-4-yl)-pyrazin-2-yl-amine,
[6-(4H-[1,2,4]), triazol-3-yl sulphanyl)-quinazolin-4-yl]-pyrazin-2-yl-amine,
[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,
(6-phenoxy-quinazolin-4-yl)-thiazolo [5,4-b] pyridin-2-yl-amine,
[6-(2-fluoro-phenoxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,
[6-(1-methyl-1H-imidazol-2-yl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,
[6-(pyridin-2-yl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,
[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-(3-methyl-[1,2,4] thiadiazol-5-yl-amine),
[6-[pyrimidin-2-yl sulphanyl]-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,
[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,
[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-thiazolo .[4,5-b] pyrazin-2-

yl-amine,
Benzthiazol-2-yl-[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-amine,
[6-(3H-[1,2,3] triazol-4-yl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,
(1-methyl-1H-pyrazol-3-yl)-[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-amine,
[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-pyrimidin-4-yl-amine,
(5-methyl-pyrazin-2-yl)-[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-amine,
[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-pyridin-2-yl-amine,
(5-chloro-thiazol-2-yl)-[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-amine,
[6-(2-fluoro-1-fluoromethyl-ethoxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,
(6-isopropoxy-quinazolin-4-yl)-pyradin-2-yl-amine,
(6-isopropoxy-quinazolin-4-yl)-thiazolo [5,4-b] pyridin-2-yl-amine,
[6-(2-hydroxy-(1S)-methyl-ethoxy-quinazolin-4-yl)]-thiazolo [5,4-b] pyridin-2-yl-amine,
(6-cyclopentyl oxy-quinazolin-4-yl)-thiazolo [5,4-b] pyridin-2-yl-amine,
[6-(2-fluoro-1-fluoromethyl-ethoxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
[6-(2-fluoro-1-fluoromethyl-ethoxy)-quinazolin-4-yl]-isoxazol-3-yl-amine,
[6-(2-fluoro-1-fluoromethyl-ethoxy)-quinazolin-4-yl]-(5-fluoro-thiazolo [5,4-b] pyridin-2-yl)-amine,
[6-(2-fluoro-1-fluoromethyl-ethoxy)-quinazolin-4-yl]-(5-methoxy-thiazolo [5,4-b] pyridin-2-yl)-amine,
[6-(4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,
(6-phenoxy-pyrido [3,2-d] pyrimidin-4-yl)-thiazol-2-yl-amine,
[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-thiazol-2-yl-amine,
[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,
[6-(5-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,
Thiazolo [5,4-b] pyridin-2-yl-[6-(3H-[1,2,3] triazol-4-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-amine,
(6-methoxy-quinazolin-4-yl)-pyrazin-2-yl-amine,
(6-hydroxy-quinazolin-4-yl)-thiazolo [5,4-b] pyridin-2-yl-amine,

6-(1-methylpyrazol-3-yl sulphanyl)-thiazolo [5,4-b] pyridin-2-yl pyrido [3,2-d] pyrimidin-4-yl-amine,
(6-ethyl sulphanyl)-thiazolo [5,4-b] pyridin-2-yl pyrido [3,2-d] pyrimidin-4-yl-amine,
(5-methoxymethyl-1,2,4-triazol-3-yl sulphanyl) thiazolo [5,4-b] pyridin-2-yl pyrido [3,2-d] pyrimidin-4-yl-amine,
(5-methylpyrazin-2-yl)-6-(1,2,4-triazol-3-yl sulphanyl) pyrido [3,2-d] pyrimidin-4-yl-amine,
6-(1-methyl imidazol-2-yl sulphanyl)-(5-methylpyrazin-2-yl) pyrido [3,2-d] pyrimidin-4-yl-amine,
6-(imidazol-2-yl sulphanyl)-(5-methylpyrazin-2-yl) pyrido [3,2-d] pyrimidin-4-yl-amine,
6-(1-ethylimidazol-2-yl sulphanyl)-(5-methylpyrazin-2-yl) pyrido [3,2-d] pyrimidin-4-yl-amine,
(5-methylpyrazin-2-yl)-6-(1-methylpyrazol-3-yl sulphanyl) pyrido [3,2-d] pyrimidin-4-yl-amine,
6-(1,5-dimethylimidazol-2-yl sulphanyl)-(5-methylpyrazin-2-yl) pyrido [3,2-d] pyrimidin-4-yl-amine,
6-(4-methyl imidazol-2-yl sulphanyl)-(5-methylpyrazin-2-yl) pyrido [3,2-d] pyrimidin-4-yl-amine,
(5-methylpyridin-2-yl)-6-(1,2,4-triazol-3-yl sulphanyl) pyrido [3,2-d] pyrimidin-4-yl-amine,
(5-fluoropyridin-2-yl)-6-(1,2,4-triazol-3-yl sulphanyl) pyrido [3,2-d] pyrimidin-4-yl-amine,
[6-(pyridin-2-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,
[6-(1,3,4-thiadiazol-2-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,
[6-(1-methyl-1H-tetrazol-5-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,
[6-(4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-3-methyl-[1,2,4] thiadiazol-5-yl-amine,
[6-(4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
(6-(3-fluoro-benzonitrile-2-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-3-methyl-[1,2,4] thiadiazol-5-yl-amine,
[6-(3H-[1,2,3] triazol-4-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
[6-(5-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-(1-methyl-

1H-pyrazol-3-yl)-amine,
[6-(3-chloro-pyridin-2-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
[6-(3-cyano-pyridin-2-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
[6-(3-amide-pyridin-2-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
6-(1H-benzimidazol-2-yl sulphanyl)-N-(1-methyl-1H-pyrazol-3-yl) pyrido (3,2-d) pyrimidin-4-yl-amine,
6-[(5-amino-4H-1,2,4-triazol-3-yl) sulphanyl]-N-(1-methyl-1H-pyrazol-3-yl) pyrido (3,2-d) pyrimidin-4-yl-amine,
N-pyrazin-2-yl-6-(4H-1,2,4-triazol-3-yl sulphanyl) pyrido (3,2-d) pyrimidin-4-yl-amine,
N-isoxazol-3-yl-6-(4H-1,2,4-triazol-3-yl sulphanyl) pyrido (3,2-d) pyrimidin-4-yl-amine,
6-{[6-(4H-1,2,4-triazol-3-yl sulphanyl) pyrido [3,2-d] pyrimidin-4-yl] amino} nicotino nitrile,
(4-methyl-1,3-thiazol-2-yl)-6-(4-methyl-1,2,4-triazol-3-yl sulphanyl)-quinazolin-4-yl-amine,
(5-methyl-1,3-thiazol-2-yl)-6-(4-methyl-1,2,4-triazol-3-yl sulphanyl)-quinazolin-4-yl-amine,
6-(methyl benzoato-2-yl) sulphanyl-thiazolo [5,4-b] pyridin-2-yl quinazolin-4-yl-amine,
6-(2-hydroxymethyl phenyl sulphanyl)-thiazolo [5,4-b] pyridin-2-yl quinazolin-4-yl-amine,
6-(pyrazin-2-yl sulphanyl)-thiazolo [5,4-b] pyridin-2-yl quinazolin-4-yl-amine,
6-(3-fluoropyridin-2-yl sulphanyl)-thiazolo [5,4-b] pyridin-2-yl quinazolin-4-yl-amine,
6-(benzoato-2-yl sulphanyl)-thiazolo [5,4-b] pyridin-2-yl quinazolin-4-yl-amine,
6-(3-chloropyridin-2-yl sulphanyl)-(1-methylpyrazol-3-yl) quinazolin-4-yl-amine,
[6-(2-dimethylamino-ethyl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,
[6-(cyclopentyl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,
[6-(2-fluorophenyl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,
[6-(2-methoxyphenyl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,
[6-(3-chloropyridin-2-yloxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,
[6-(3-cyanopyridin-2-yloxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,
[6-(3-carboxamide pyridin-2-yloxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,
[6-(pyridin-2-yloxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,
[6-(3-methylpyridin-2-yloxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,
[6-(methylcarbamoyl-methyl oxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,

[6-(3-methylsulfonyl pyridin-2-yloxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,
[6-(3-chloropyridin-2-yloxy)-quinazolin-4-yl]-3-methyl-[1,2,4] thiadiazol-5-yl-amine,
[6-(3-fluoropyridin-2-yloxy)-quinazolin-4-yl]-3-methyl-[1,2,4] thiadiazol-5-yl-amine,
[6-(3-chloropyridin-2-yloxy)-quinazolin-4-yl]-pyridin-2-yl-amine,
[6-(tetrahydro-2H-pyran-4-yloxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
[6-(3,5-difluoro pyridin-2-yloxy)-quinazolin-4-yl]-3-methyl-[1,2,4] thiadiazol-5-yl-amine,
[6-(2-chloro-6-(methylsulfonyl) phenoxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
[6-(2,4-difluoro phenoxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
[6-(2-fluoro-6-(5-methyl-[1,2,4] oxadiazol-3-yl) phenoxy)-quinazolin-4-yl]-3-methyl-[1,2,4] thiadiazol-5-yl-amine,
[6-(2-fluoro-4-(methylsulfonyl phenoxy)-quinazolin-4-yl]-3-methyl-[1,2,4] thiadiazol-5-yl-amine,
[6-(2-fluoro-6-(methylsulfonyl) phenoxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
[6-(2-fluoro-6-(methylsulfonyl) phenoxy)-quinazolin-4-yl]-(1-ethyl-1H-pyrazol-3-yl)-amine,
[6-(2-fluoro-6-(methylsulfonyl) phenoxy)-quinazolin-4-yl]-pyrazin-2-yl-amine,
[6-(2-chloro-6-(methanesulphonyl amino) phenoxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
3-fluoro-2-({4-[[pyrazin-2-yl] amino] quinazolin-6-yl} oxy) benzonitrile,
[6-(butyl lactone-2-yloxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
[6-(2,4-difluoro-6-(methylsulfonyl) phenoxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
[6-(2-fluoro-6-(methylsulfonyl) phenoxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,
N-(1-methyl-1H-pyrazol-3-yl)-6-[2-(methylsulfonyl) phenoxy] quinazolin-4-yl-amine,
3-fluoro-2-({4-[[5-methylpyrazin-2-yl] amino] quinazolin-6-yl) oxy) benzonitrile,
6-(3-chloropyridin-2-yl sulphanyl)-(1-methylpyrazol-3-yl) quinazolin-4-yl-amine,
6-(3-chloropyridin-2-yl sulphanyl)-(5-methyl-pyrazin-2-yl) quinazolin-4-yl-amine,
6-(3-chloropyridin-2-yl sulphanyl)-(1H-pyrazol-3-yl) quinazolin-4-yl-amine,
6-(acetyl piperidin-4-yl) oxy-N-[1,3] thiazolo [5,4-d] pyridin-2-yl quinazolin-4-yl-amine,
N-(1-methyl-1H-pyrazol-3-yl)-6-(pyrazin-2-yloxy) quinazolin-4-yl-amine,
N-(1-methyl-1H-pyrazol-3-yl)-6-(pyrimidin-4-yloxy) quinazolin-4-yl-amine,
6-[2-fluoro-1-(fluoromethyl) ethoxy]-N-[1,3] thiazolo [5,4-d] pyrimidin-2-yl quinazolin-4-

yl-amine,
6-[(3-chloropyridin-2-yl) oxy]-N-1,3-thiazol-2-yl quinazolin-4-amine (1-methylpyrazol-3-yl) quinazolin-4-yl-amine,
6-(1,3-benzothiazol-2-yloxy)-N-(1-methyl-1H-pyrazol-3-yl) quinazolin-4-yl-amine,
N-(1-methyl-1H-pyrazol-3-yl)-6-(quinazolin-2-yloxy) quinazolin-4-yl-amine,
6-[(5-fluoropyridin-2-yl) oxy]-N-(1-methyl-1H-pyrazol-3-yl) quinazolin-4-yl-amine,
6-[(3-chloropyridin-2-yl) oxy]-N-(5-methyl-1H-pyrazol-3-yl) quinazolin-4-yl-amine,
N-(1-methyl-1H-pyrazol-3-yl)-6-(pyridin-3-yloxy) quinazolin-4-yl-amine,
6-[(3-chloropyridin-2-yl) oxy]-N-4H-[1,2,4]-triazol-3-yl quinazolin-4-yl-amine,
6-[(5-fluoropyridin-3-yl) oxy]-N-(1-methyl-1H-pyrazol-3-yl) quinazolin-4-yl-amine,
6-[(3-chloropyridin-2-yl) oxy]-N-[1,2,4]-thiadiazole-5-yl quinazolin-4-yl-amine,
N-(1-methyl-1H-pyrazol-3-yl)-6-[(3-methylpyridin-2-yl) oxy] quinazolin-4-yl-amine,
6-{[3-(difluoromethyl) pyridin-2-yl] oxy}-N-(1-methyl-1H-pyrazol-3-yl) quinazolin-4-yl-amine,
N-(1-methyl-1H-pyrazol-3-yl)-6-{[3-(trifluoromethyl) pyridin-2-yl] oxy} quinazolin-4-yl-amine,
[2-({4-[[1-methyl-1H-pyrazol-3-yl] amino] quinazolin-6-yl} oxy) pyridin-3-yl] methanol,
6-{[3-(fluoromethyl) pyridin-2-yl] oxy}-N-(1-methyl-1H-pyrazol-3-yl) quinazolin-4-yl-amine,
1-[2-({4-[[1-methyl-1H-pyrazol-3-yl] amino] quinazolin-6-yl} oxy) pyridine 3-yl] ethanone,
5-chloro-2-methyl-4-({4-[[1-methyl-1H-pyrazol-3-yl] amino] quinazolin-6-yl} oxy) pyridazin-3 (2H)-one,
6-[(6-fluoropyridin-2-yl) oxy]-N-(1-methyl-1H-pyrazol-3-yl) quinazolin-4-yl-amine,
[3-fluoro-2-({4-[[1-methyl-1H-pyrazol-3-yl] amino] quinazolin-6-yl} oxy) phenyl] methanol,
6-[2-fluoro-6-(fluoromethyl) phenoxy]-N-(1-methyl-1H-pyrazol-3-yl) quinazolin-4-yl-amine,
[3-chloro-4-({4-[[1-methyl-1H-pyrazol-3-yl] amino] quinazolin-6-yl} oxy) phenyl] methanol,
Methyl-5-(methylsulfonyl)-2-({4-[[3-methyl-[1,2,4]-thiadiazol-5-yl] amino] quinazolin-6-yl} oxy) benzoate,
3-fluoro-2-({4-[[1-pyridin-2-yl-1H-pyrazol-3-yl] amino] quinazolin-6-yl} oxy) benzonitrile,
1-[3-fluoro-2-({4-[[1-methyl-1H-pyrazol-3-yl] amino] quinazolin-6-yl} oxy) phenyl] ethanone,

6-[(3-chloropyridin-2-yl) oxy]-N-[1-(difluoromethyl)-1H-pyrazol-3-yl] quinazolin-4-yl-amine,
3-chloro-N,N-dimethyl-2-({4-[[3-methyl-[1,2,4]-thiadiazol-5-yl] amino] quinazolin-6-yl} oxy) benzenesulphon amide,
6-[2-chloro-6-(ethylsulfonyl) phenoxy]-N-(3-methyl-1,2,4-thiadiazol-5-yl) quinazolin-4-yl-amine,
6-[2-fluoro-6-(methylsulfonyl) phenoxy]-N-(5-methylpyrazin-2-yl) quinazolin-4-yl-amine,
6-[2-chloro-6-(cyclopropyl sulfonyl) phenoxy]-N-(1-methyl-1H-pyrazol-3-yl) quinazolin-4-yl-amine,
6-[2-fluoro-6-(methylsulfonyl) phenoxy]-N-1H-pyrazol-3-yl quinazolin-4-yl-amine,
6-[3-cyclopropyl pyridin-2-yl] oxy]-N-(1-methyl-1H-pyrazol-3-yl) quinazolin-4-yl-amine,
[2-({4-[(1-methyl-1H-pyrazol-3-yl) amino] quinazolin-6-yl} oxy)-3-(trifluoromethyl) phenyl] methanol,
6-[2-fluoro-6-(methylsulfonyl) phenoxy]-N-pyridazin-3-yl quinazolin-4-yl-amine,
N-(5-chloropyrazin-2-yl)-6-[2-fluoro-6-(methylsulfonyl) phenoxy] quinazolin-4-yl-amine,
[3,5-difluoro-4-({4-[(1-methyl-1H-pyrazol-3-yl) amino] quinazolin-6-yl} oxy) phenyl] methanol,
3-fluoro-2-({4-[(1-methyl-1H-pyrazol-5-yl) amino] quinazolin-6-yl} oxy) benzonitrile,
6-[4-methyl-2-(methylsulfonyl) phenoxy]-N-(1-methyl-1H-pyrazol-3-yl) quinazolin-4-yl-amine,
6-(2,6-difluoro phenoxy)-N-(1-methyl-pyrazol-3-yl) quinazolin-4-yl-amine,
1-[3-methyl-2-([4-[(1-methyl-pyrazol-3-yl) amino] quinazolin-6-yl] oxy) phenyl] ethanone,
6-[2-(fluoromethyl)-6-(methylsulfonyl) phenoxy]-N-(1-methyl-pyrazol-3-yl) quinazolin-4-yl-amine,
3-methyl-2-({4-[(1-methyl-pyrazol-3-yl) amino] quinazolin-6-yl} oxy) benzonitrile,
Cyclopropyl [3-fluoro-2-([4-[{1-methyl-pyrazol-3-yl} amino] quinazolin-6-yl] oxy) phenyl] methanone,
6-[2-fluoro-6-(methoxymethyl) phenoxy]-N-(1-methyl-pyrazol-3-yl) quinazolin-4-yl-amine,
[6-(5-chloro-3-fluoropyridin-2-yloxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
[6-(3-fluoropyridin-2-yloxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
6-[2-methyl-6-(methylsulfonyl) phenoxy]-N-(1-methyl-pyrazol-3-yl) quinazolin-4-yl-amine,
6-[2-(fluoromethyl)-6-(methylsulfonyl) phenoxy]-N-(1H-pyrazol-3-yl) quinazolin-4-yl-amine or
[6-(2-fluoro-6-(methane sulfonamide) phenoxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-

yl)-amine.

Compound of the aforesaid (a)-(i) or pharmacologically acceptable salts thereof have glucokinase activation action. In other words, this invention puts forward glucokinase activator consisting of compound in accordance with (a)-(i) or pharmacologically acceptable salts thereof.

About 10 years ago, the hypothesis was proposed that glucokinase should work as glucose sensor of liver and pancreas β cell (cf. for example, Garfinkel D et al., "Computer modeling identifies glucokinase as glucose sensor of pancreatic β-cells", American Journal Physiology, Vol. 247 (3Pt2), 1984, p527-536). In practice, from results of recent glucokinase genenetically modified mouse, it is becoming clear that glucokinase carries out important role in glucose homeostasis of whole body. The mouse whose glucokinase gene has been destroyed dies soon after birth (cf. for example Grupe A et al. "Transgenic knockouts reveal a critical requirement for pancreatic β cell glucokinase in maintaining glucose homeostasis" Cell, Vol. 83, 1995, p69-78,), while on the other hand normal and diabetes mellitus mouse that overexpressed glucokinase had blood glucose level which became lower (cf. for example Ferre T et al. "Correction of diabetic alterations by glucokinase", Proceedings of the National Academy of Sciences of the U.S.A., Vol. 93, 1996, p7225-7230). The reaction of hepatocyte and pancreas β cell to glucose concentration rise differs, but in each case corresponds to the direction of lower blood glucose. The pancreas β cell starts to secrete more insulin, and at the same time liver takes in sugar to store as glycogen, so sugar release is also lowered.

In this way variation of glucokinase enzyme activity performs important role in glucose homeostasis of mammal through liver and pancreas β cell. A spontaneous mutation of the glucokinase gene has been discovered in a case in which diabetes mellitus developed in the young, known as MODY2 (maturity-onset diabetes of the young), wherein fall of glucokinase activity caused blood glucose to increase (cf. for example Vionnet N et al., "Nonsense mutation in the glucokinase gene causes early-onset non-insulin-dependent diabetes mellitus", Nature Genetics, Vol. 356, 1992, p721-722). On the other hand, the lineage having spontaneous mutation which increases glucokinase activity is also found, and such persons exhibit symptoms of hypoglycemia (cf. for example, Glaser B et al.,

"Familial hyperinsulinism caused by an activating glucokinase mutation", New England Journal Medicine, Vol. 338, 1998, p226-230).

These findings show that glucokinase works as a glucose sensor in humans, and performs an important role in glucose homeostasis. On the other hand, in many type II diabetics, blood glucose control using glucokinase sensor system is regarded as possible. The compound in accordance with (a)-(i) of this invention, or the pharmacologically acceptable salts thereof, are expected to be useful as therapy and/or preventative agent of type II diabetes, since insulin secretion facilitation action of pancreas β cell, and sugar intake facilitation and sugar release inhibitory action of liver can be expected for glucokinase activators.

Moreover, recently, it has become clear that pancreas β cell type glucokinase was also expressed localised in rat brain, particularly in the feeding centre (Ventromedial hypothalamus, below abbreviated to "VMH"). About 20% of the neuron of the VMH, known as glucose responsive neuron, are considered to play an important role body weight control from before. When glucose is administered into rat brain, the quantity of food consumed falls, and in contrast to this, when glucose metabolism is suppressed by intracerebral administration of the glucose analog glucosamine, the quantity food consumed becomes excessive. From electrophysiological experiments, it has been recognized that glucose responsive neuron is activated in response to physiological glucose concentration change (5-20 mM), but activity is suppressed when glucose metabolism is inhibited by glucosamine and the like. In glucose concentration perception system of VHM, the mechanism is assumed to be through glucokinase as it is in insulin secretion of pancreas β cell.

From these findings, it is considered that the substance having glucokinase activation action of VHM as well as liver and pancreas β cell can have blood glucose correction effect, and in addition to this, can correct obesity which is problem with many type II diabetes patients, and compound in accordance with this invention is expected to be useful not only in type I diabetes, but also in type II diabetes in which prior art diabetes mellitus drug cannot achieved satisfactory blood glucose level lowering.

Accordingly, the compound in accordance with (a)-(i) of this invention or the pharmacologically acceptable salts thereof is considered to be useful in therapy and/or prevention of obesity.

In accordance with the above, compound in accordance with (a)-(i) of this invention or pharmacologically acceptable salts thereof have glucokinase activation action and are useful as diabetes therapy and/or preventative agent, or as therapy and/or preventative agent of chronic complication of diabetes mellitus such as retinopathy, nephropathy, neuropathy, ischemic cardiac disease, arteriosclerosis or the like. Further it is useful as therapy and/or preventative agent of obesity.

Here, complication of diabetes mellitus means disease which develops due to onset of diabetes mellitus, for example diabetic nephropathy, diabetic retinopathy, diabetic neuropathy or diabetic arteriosclerosis and the like are nominated as complication of such diabetes mellitus.

Ideal form for Carrying Out the Invention

Firstly, meaning of term used in this specification is described, and thereafter it is described about compound in accordance with this invention.

As "aryl group", hydrocarbon ring aryl group and the like of carbon number 6-14 may be proposed. For example, phenyl group or naphthyl group and the like may be proposed.

As "lower alkyl group", alkyl group containing 1-6 C straight chain or branched chain is denoted, for example methyl group, ethyl group, propyl group, isopropyl group, butyl group, isobutyl group, sec-butyl group, tert-butyl group, pentyl group, isoamyl group, neopentyl group, isopentyl group, 1,1-dimethylpropyl group, 1-methylbutyl group, 2-methylbutyl group, 1,2-dimethylpropyl group, hexyl group, isohexyl group, 1-methyl pentyl group, 2-methyl pentyl group, 3-methyl pentyl group, 1,1-dimethylbutyl group, 1,2-dimethylbutyl group, 2,2-dimethyl butyl group, 1,3-dimethyl butyl group, 2,3-dimethylbutyl group, 3,3-dimethylbutyl group, 1-ethyl butyl group, 2-ethyl butyl group, 1,2,2-trimethylpropyl group, 1-ethyl-2-methylpropyl group and the like may be proposed.

As "cycloalkyl group", 3-7 C cycloalkyl group is denoted, for example cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, cycloheptyl group may be proposed.

As "lower alkenyl group", 1-6 C straight or branched chain lower alkenyl group is denoted, and for example, vinyl group, allyl group, 1-butenyl group, 2-butenyl group, 1-pentenyl group and the like may be proposed.

As "lower alkoxy group", denotes group wherein hydrogen atom of hydroxy group substituted by the aforesaid lower alkyl group, for example methoxy group, ethoxy group, propoxy group, isopropoxy group, butoxy group, sec-butoxy group, tert butoxy group, pentyloxy group, isopentyloxy group, hexyloxy group or isohexyloxy group and the like may be proposed.

As "heteroaryl group". 5-6 membered monocycle containing 1-3 of heteroatom selected from the group comprising oxygen atom, sulfur atom and nitrogen atom in ring is denoted, or bicyclic heteroaryl group in which said monocyclic heteroaryl group and pyridine ring or benzene were condensed is denoted, for example furyl group, thienyl group, pyrrolyl group, imidazolyl group, triazolyl group, thiazolyl group, thiadiazolyl group, isothiazolyl group, oxazolyl group, isoxazolyl group, pyridyl group, pyrimidinyl group, pyridazinyl group, pyrazolyl group, pyrazinyl group, quinolinyl group, isoquinolinyl group, quinazolinyl group, quinolizinyl group, quinoxalinyl group, cinnolinyl group, benzimidazolyl group, imidazo pyridyl group, benzofuranyl group, naphthyridinyl group, 1,2-benzo isoxazolyl group, benzoxazolyl group, benzothiazolyl group, oxazolo pyridyl group, thiazolo pyridyl group, thiazolo pyrazinyl group, isothiazolo pyridyl group, benzothienyl group and the like may be proposed.

"halogen atom" denotes for example fluorine atom, chlorine atom, bromine atom and iodine atom.

"hydroxyalkyl group" denotes group wherein one hydrogen atom of the said lower alkyl group is substituted by hydroxy group, for example hydroxymethyl group, 2-hydroxyethyl group, 1-hydroxypropyl group, 1-hydroxyethyl group, 2-hydroxypropyl group, 2-hydroxy-

1-methyl-ethyl group and the like may be proposed.

"amino alkyl group" denotes group wherein one hydrogen atom of the said lower alkyl group is substituted by amino group for example aminomethyl group, amino ethyl group, aminopropyl group and the like may be proposed.

"alkanoyl group" denotes combined group of the aforesaid lower alkyl group and carbonyl group, for example methyl carbonyl group, ethyl carbonyl group, propyl carbonyl group, isopropyl carbonyl group and the like may be proposed.

"alkoxycarbonyl group" denotes group wherein hydrogen atom of carboxyl group is substituted by the aforesaid lower alkyl group, for example methoxycarbonyl group, ethoxycarbonyl group, propyl carbonyl group, isopropyl carbonyl group and the like may be proposed.

"lower alkyl sulphonyl group" denotes combined group of the aforesaid lower alkyl group and sulphonyl group, for example methylsulfonyl group, ethylsulfonyl group, propyl sulphonyl group, isopropyl sulphonyl group and the like may be proposed.

"cycloalkyl sulphonyl group" denotes combined group of the aforesaid cycloalkyl group and sulphonyl group, for example cyclopropyl sulphonyl group, cyclobutyl sulphonyl group, cyclopentyl sulphonyl group and the like may be proposed.

"mono lower alkyl carbamoyl group" denotes carbamoyl group mono substituted by the aforesaid lower alkyl group, for example methylcarbamoyl group, ethyl carbamoyl group, propyl carbamoyl group, isopropyl carbamoyl group, butyl carbamoyl group, sec-butyl carbamoyl group, tert-butyl carbamoyl group and the like may be proposed.

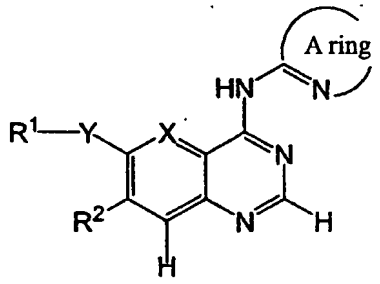
"dilower alkyl carbamoyl group" denotes carbamoyl group disubstituted by same or different aforesaid lower alkyl group, for example, dimethylcarbamoyl group, diethylcarbamoyl group, ethylmethyl carbamoyl group, dipropyl carbamoyl group, methylpropyl carbamoyl group, diisopropyl carbamoyl group and the like may be proposed.

"mono lower alkyl amino group" denotes amino group mono substituted by the aforesaid lower alkyl group, for example methylamino group, ethylamino group, propylamino group, isopropyl-amino group, butyl amino group, sec-butylamino group or tert-butylamino group and the like may be proposed.

"dilower alkyl amino group" denotes amino group disubstituted by the same or different aforesaid lower alkyl group, for example dimethylamino group, diethylamino group, dipropylamino group, methylpropyl amino group or diisopropylamino group and the like may be proposed.

As "amino alkyl group" for example, aminomethyl group, 1-amino ethyl group, 2-amino ethyl group and the like may be proposed.

Afterwards, in order to disclose more specifically the compound represented by formula (I) in accordance with this invention, the symbols used in Formula (I) are explained



(I)

(wherein, each symbol is the same as above).

R1 denotes one atom or group arbitrarily selected from the following (1), (2), (3), (4), (5) and (6).

(1). 5-6 membered heteroaryl group containing 1-3 heteroatoms selected from the group comprising nitrogen atom, sulfur atom and oxygen atom in ring (said heteroaryl group may form condensed ring with phenyl group),
(2). Aryl group,

(3). The lower alkyl group that is linear or branched,
(4). 3-7 C cycloalkyl group (1 or 2 of the carbon atoms (excluding the carbon atom bonded to Y) constituting said group may be replaced by oxygen atom, nitrogen atom, N-alkanoyl group or carbonyloxy group, moreover may have 1 or 2 double bonds in the ring),
(5). Straight or branched chain lower alkenyl group,
(6). Hydrogen atom.

When R1 denotes "5-6 membered heteroaryl group with 1-3 contain heteroatom selected from the group comprising nitrogen atom, sulfur atom and oxygen atom in ring", for example isothiazolyl group, imidazolyl group, oxazolyl group, thiadiazolyl group, thienyl group, triazolyl group, tetrazolyl group, pyridyl group, pyrimidinyl group, furyl group, thiazolyl group, isoxazolyl group or pyrazolyl group and the like are proposed. Among these, triazolyl group, imidazolyl group, thiazolyl group, pyridyl group are preferred, and triazolyl group is more preferred.

Moreover, said heteroaryl group may form 9-10 membered bicyclic heteroaryl group by condensing with same or different heteroaryl group or aryl group.

As 9-10 membered bicyclic heteroaryl group, for example, isoquinolyl group, isoindolyl group, indolyl group, quinolyl group, thiazolo pyridyl group, thiazolo pyrazinyl group, benzimidazolyl group, benzoxazolyl group, benzothiazolyl group, benzotriazolyl group, benzofuranyl group, imidazo pyridinyl group, tri azo pyridinyl group and the like may be proposed.

As "the aryl group" denoted by R1, as embodiments for example, phenyl group, naphthyl group, biphenyl group and the like may be proposed. Among these, phenyl group or naphthyl group is preferred, and phenyl group is more preferred.

As "straight or branched chain lower alkyl group" denoted by R1, for example, methyl group, ethyl group, propyl group, isopropyl group and the like may be proposed.

As "3-7 C cycloalkyl group" denoted by R1, a group same as cycloalkyl group of the said definition is denoted, or 1 or 2 of the carbon atoms (excluding the carbon atom bonded to

Y) constituting said group may be replaced by oxygen atom, nitrogen atom, N-alkanoyl group or carbonyloxy group, moreover group may have 1 or 2 double bonds in the ring,

As said R1, for example, tetrahydrofuranyl group, tetrahydropyranyl group, pyrrolidinyl group, piperidinyl group, N-acetyl piperidinyl group, 3,4-dihydropyridazinyl group and the like are proposed. Among these, tetrahydrofuranyl group, tetrahydropyranyl group, N-acetyl piperidinyl group or 3,4-dihydropyridazinyl group and the like are preferred.

As "straight chain or branched lower alkenyl group" denoted by R1, for example, propenyl group, isopropenyl group, isobutenyl group are preferred, and isopropenyl group is more preferred.

As R1, among the aforesaid (1) to (6),
(1). 5-6 membered heteroaryl group which contains 1-3 of heteroatom selected from the group comprising nitrogen atom, sulfur atom and oxygen atom in ring (said heteroaryl group may form condensed ring with phenyl group),
(2). Aryl group,
(3). Straight or branched chain lower alkyl group,
(4). 3-7 C cycloalkyl group (1 or 2 of the carbon atoms (excluding the carbon atom bonded to Y) constituting said group may be replaced by oxygen atom, nitrogen atom, N-alkanoyl group or carbonyloxy group, moreover may have 1 or 2 double bonds in the ring),
is preferred, and

(1). 5-6 membered heteroaryl group which contains 1-3 of heteroatom selected from the group comprising nitrogen atom, sulfur atom and oxygen atom in ring (said heteroaryl group may form condensed ring with phenyl group),
(2). Aryl group is more preferred.

Moreover, when R1 is the aforesaid (1) to (5), R1 may be substituted by 1-3 same or different groups selected from the following substituent group α.

Substituent group α: Lower alkyl group (the said lower alkyl group may be substituted by 1-3 halogen atoms), 3-7 C cycloalkyl group, lower alkoxy group, hydroxy group,

hydroxyalkyl group (hydrogen atom of hydroxy group in said hydroxyalkyl group may be substituted by lower alkyl group), alkanoyl group, halogen atom, oxo group, lower alkyl sulphonyl group, lower alkyl sulfonyl amino group, mono- or di-lower alkyl carbamoyl group, mono- or di-lower alkyl carbamoyl alkyl group, mono- or di-lower alkyl sulphamoyl group, amino group, mono- or di- lower alkyl amino group, cyano group, and 5-6 membered heteroaryl group with 1-3 heteroatoms selected from the group comprising nitrogen atom, sulfur atom and oxygen atom in ring.

"lower alkyl group" as said substituent, denotes the same group with the same meaning as aforesaid lower alkyl group, or group in which lower alkyl group of the said definition of the said definition is substituted by 1-3 halogen atoms.

As said lower alkyl group, for example, methyl group, ethyl group, isopropyl group, propyl group, 2-fluoro-1-fluoromethyl-ethyl group, trifluoromethyl group or fluoromethyl group and the like may be proposed.

As "3-7 C cycloalkyl group" of said substituent, group same as in cycloalkyl group of the said definition is denoted, and as embodiments for example cyclopropyl group, cyclobutyl group, cyclopentyl group and the like may be proposed.

As "lower alkoxy group" of said substituent, group same as in lower alkoxy group of the said definition is denoted, and as embodiments for example methoxy group, ethoxy group, isopropoxy group, propoxy group and the like may be proposed.

As "hydroxy lower alkyl group" of said substituent, group same as in hydroxyalkyl group of the said definition is denoted or denotes group wherein hydrogen atom of hydroxy group in hydroxyalkyl group of the said definition is substituted by lower alkyl group, and as embodiments for example 2-hydroxyethyl group, 1-hydroxypropyl group or 1-hydroxyethyl group, methoxy methyl group or ethoxymethyl group and the like may be proposed.

As "alkanoyl group" of said substituent, group same as alkanoyl group of the said definition is denoted, or denotes group wherein the carbonyl group is bonded to cycloalkyl of the said definition, and as embodiments for example methyl carbonyl group, ethyl carbonyl

group, propyl carbonyl group, isopropyl carbonyl group, cyclopropylcarbonyl group and the like may be proposed.

As "halogen atom" of said substituent, group same as in halogen atom of the said definition is denoted, and as embodiments for example fluorine atom, chlorine atom, bromine atom and the like may be proposed.

As "lower alkyl sulphonyl group" of said substituent, group same as in lower alkyl sulphonyl group of the said definition is denoted, and as embodiments for example methylsulfonyl group, ethylsulfonyl group, propyl sulphonyl group, isopropyl sulphonyl group and the like may be proposed.

As "lower alkyl sulfonyl amino group" of said substituent, combined group of lower alkyl sulphonyl group and amino group of the said definition, and as embodiments for example methylsulphonylamino group, ethane sulfonyl amino group, isopropyl sulfonyl amino group and the like may be proposed.

As "mono lower alkyl carbamoyl group" of said substituent, group same as in mono lower alkyl carbamoyl group of the said definition is denoted, and as embodiments for example methylcarbamoyl group, ethyl carbamoyl group, propyl carbamoyl group, isopropyl carbamoyl group, butyl carbamoyl group, sec-butyl carbamoyl group, tert-butyl carbamoyl group and the like may be proposed.

As "dilower alkyl carbamoyl group" of said substituent, group same as in dilower alkyl carbamoyl group of the said definition is denoted, and as embodiments for example dimethylcarbamoyl group, diethylcarbamoyl group, ethylmethyl carbamoyl group, dipropyl carbamoyl group, methylpropyl carbamoyl group, diisopropyl carbamoyl group and the like may be proposed.

As "mono lower alkyl carbamoyl alkyl group" of said substituent, is denoted combined group of mono lower alkyl carbamoyl group and alkyl group of the said definition, and as embodiments for example methylcarbamoyl methyl group, ethyl carbamoylmethyl group, propyl carbamoylmethyl group and the like may be proposed.

As "dilower alkyl carbamoyl alkyl group" of said substituent, is denoted combined group of dilower alkyl carbamoyl group and alkyl group of the said definition, and as embodiments for example dimethylcarbamoylmethyl group, diethylcarbamoyl methyl group, ethylmethyl carbamoylmethyl group and the like may be proposed.

As "mono lower alkyl sulphamoyl group" of said substituent, is denoted group wherein one hydrogen atom in NH of sulphamoyl group is substituted by the aforesaid lower alkyl group, and as embodiments for example methyl sulphamoyl group, ethyl sulphamoyl group, isopropyl sulphamoyl group and the like may be proposed.

As "dilower alkyl sulphamoyl group" of said substituent, is denoted group wherein two hydrogen atoms in NH of sulphamoyl group was substituted by the same or different aforesaid lower alkyl group, and as embodiments for example dimethyl sulphamoyl group, ethylmethyl sulphamoyl group, diethyl sulphamoyl group, diisopropyl sulphamoyl group and the like may be proposed.

As "mono lower alkyl amino group" of said substituent, group same as in mono lower alkyl amino group of the said definition is denoted, and as embodiments for example methylamino group, ethylamino group, propylamino group, isopropyl-amino group and the like may be proposed.

As "dilower alkyl amino group" of said substituent, group same as in dilower alkyl amino group of the said definition is denoted, and as embodiments for example dimethylamino group, diethylamino group, dipropylamino group, methylpropyl amino group and the like may be proposed.

Y denotes an oxygen atom or sulfur atom.

In accordance with the above, as embodiments, as -Y-R1, it is for example [1,2,4] triazol-3-yl sulphanyl group,
4-methyl-[1,2,4] triazol-3-yl sulphanyl group,
5-methyl-[1,2,4] triazol-3-yl sulphanyl group,

5-methoxymethyl-[1,2,4] triazol-3-yl sulphanyl group,
5-amino-[1,2,4] triazol-3-yl sulphanyl group,
[1,2,3] triazol-3-yl sulphanyl group,
[1,3,4] thiadiazol-3-yl sulphanyl group,
1-ethyl-imidazol-2-yl sulphanyl group,
1-methyl-imidazol-2-yl sulphanyl group,
1,5-dimethyl-imidazol-2-yl sulphanyl group,
Imidazol-2-yl sulphanyl group,
3-methyl-imidazol-2-yl sulphanyl group,
1-methylpyrazol-3-yl sulphanyl group,
Pyridin-2-yl sulphanyl group,
Pyrimidin-2-yl sulphanyl group,
Pyrazin-2-yl sulphanyl group,
3-cyanopyridin-2-yl sulphanyl group,
3-carbamoylpyridin-3-yl sulphanyl group,
3-fluoropyridin-3-yl sulphanyl group,
3-chloropyridin-3-yl sulphanyl group,
1-methyl-1H-tetrazol-5-yl sulphanyl group,
Phenyl sulphanyl group,
2-fluorophenyl sulphanyl group,
2-methoxycarbonylphenyl sulphanyl group,
2-cyanophenyl sulphanyl group,
2-methoxyphenyl sulphanyl group,
2-hydroxymethyl phenyl sulphanyl group,
Benzoic acid-2-yl sulphanyl group,
Methyl sulphanyl group,
Ethyl sulphanyl group,
Isopropyl sulphanyl group,
Cyclopentyl sulphanyl group,
Cyclohexyl sulphanyl group,
2-dimethylamino-ethyl sulphanyl group,
Benzimidazol-2-yl sulphanyl group,
3-chloropyridin-2-yloxy group,

4-chloropyridin-2-yloxy group,

3-carbamoylpyridin-2-yloxy group,

3-cyanopyridin-2-yloxy group,

3-methylpyridin-2-yloxy group,

3-methylsulfonyl pyridin-2-yloxy group,

3-difluoromethyl pyridin-2-yloxy group,

Pyridin-2-yloxy group,

Pyridin-3-yloxy group,

4-trifluoromethyl-pyridin-3-yloxy group,

3-hydroxymethyl-pyridin-2-yloxy group,

3-fluoromethyl-pyridin-2-yloxy group,

3-cyclopropyl-pyridin-2-yloxy group,

3-methoxycarbonyl pyridin-2-yloxy group,

3-fluoropyridin-2-yloxy group,

5-fluoropyridin-2-yloxy group,

5-fluoropyridin-3-yloxy group,

2,5-difluoro pyridin-2-yloxy group,

3,5-chloro-3-fluoropyridin-2-yloxy group,

Pyrimidin-2-yloxy group,

Pyrazin-2-yloxy group,

Phenoxy group,

2-fluoro phenoxy group,

2,4-dichlorophenoxy group,

2,6-difluoro phenoxy group,

2-acetyl-6-methylphenoxy group,

2-fluoro-6-hydroxymethyl phenoxy group,

2-fluoro-6-fluoromethyl phenoxy group,

2-cyano-6-fluoro phenoxy group,

2-cyano-6-methylphenoxy group,

2-chloro-4-hydroxymethyl phenoxy group,

2-acetyl-6-fluoro-phenoxy group,

2-chloro-6-methylsulfonyl phenoxy group,

2-chloro-6-ethane sulfonyl phenoxy group,

2-chloro-6-cyclopropyl sulfonyl phenoxy group,

2-methylsulfonyl phenoxy group,

2-fluoro-6-methylsulfonyl phenoxy group,

2-fluoro-4-methylsulfonyl phenoxy group,

2-fluoromethyl-6-methylsulfonyl phenoxy group,

2-methylsulfonyl-4-methylphenoxy group,

4-methylsulfonyl 2-methoxycarbonyl phenoxy group,

2-cyclopropylcarbonyl-6-fluoro phenoxy group,

2-chloro-6- (methylsulphonylamino) phenoxy group,

2,6-difluoro-4-hydroxymethyl phenoxy group,

2-fluoro-6-(5-methyl-[1,2,4] oxadiazol-3-yl) phenoxy group,

Ethoxy group,

Isopropoxy group,

2-methoxy-1-methyl-ethoxy group,

1-methoxymethyl-propoxy group,

3-hydroxy-1-methyl-propoxy group,

1-hydroxymethyl-propoxy group,

2-amino-1-ethoxy group,

2-hydroxy-propoxy group,

2-methoxy propoxy group,

2-hydroxy-1-methyl-ethoxy group,

2-hydroxy-ethoxy group,

2-dimethylamino-1-methyl-ethoxy group,

2-fluoro-1-fluoromethyl-ethoxy group,

2-fluoro-1-methyl-ethoxy group,

Methylcarbamoyl methyl oxy group,

Cyclopentyl oxy group,

Cyclohexyl oxy group,

Cycloheptyl oxy group,

2-hydroxy-cyclopentyl oxy group,

Tetrahydropyran-4-yloxy group,

Butyrolactone-2-yloxy group,

1-acetyl piperidin-4-yloxy group,

3-allyloxy group,
3-isopropenyl oxy group,
1-methyl-allyloxy group,
Hydroxy group,
Benzothiazol-2-yloxy group,
quinazolin-2-yloxy group,
5-chloro-2-methyl-3-oxo-2,3-dihydropyridazin-4-yloxy group, and the like may be proposed.

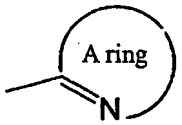
Among these, for example, cyclopentyl oxy group, isopropoxy group, 2-methoxy-1-methyl-ethoxy group, 2-hydroxy-1-methyl-ethoxy group, 2-fluoro-1-fluoromethyl-ethoxy group, phenyl-sulphanyl group, phenoxy group, 2-fluoro-phenoxy group, 4H-[1,2,4] triazol-3-yl sulphanyl group, 5-methyl-[1,2,4] triazol-3-yl sulphanyl group, 4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl group, 3H-[1,2,3] triazol-4-yl sulphanyl group, imidazol-2-yl sulphanyl group, pyridin-2-yl sulphanyl group, 1-methylpyrazol-3-yl sulphanyl group, 3-chloropyridin-2-yloxy group, 2-fluoro-6- (methylsulfonyl) phenoxy group, 2-chloro-6-(methylsulphonylamino) phenoxy group, 5-chloro-2-methyl-3-oxo-2,3-dihydropyridazin-4-yloxy group, 2-fluoro-6-fluoromethyl phenoxy group, 2-cyano-6-fluoro phenoxy group, 2-fluoro-6-methylsulfonyl phenoxy group, 2,6-difluoro-4-hydroxymethyl phenoxy group, 2,6-difluoro phenoxy group, 2-fluoromethyl-6-methylsulfonyl phenoxy group, 2-cyclopropylcarbonyl-6-fluoro phenoxy group, 3-fluoropyridin-2-yloxy group and the like are preferred, and
2-hydroxy-1-methyl-ethoxy group, 2-fluoro-1-fluoromethyl-ethoxy group, 2-fluoro-phenoxy group, 4H-[1,2,4] triazol-3-yl sulphanyl group, 5-methyl-[1,2,4] triazol-3-yl sulphanyl group, 4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl group, 2-fluoro-6-(methylsulfonyl) phenoxy group, 2-chloro-6- (methylsulphonylamino) phenoxy group, 3-chloropyridin-2-yloxy group, 5-chloro-2-methyl-3-oxo-2,3-dihydropyridazin-4-yloxy group,
2-fluoro-6-fluoromethyl phenoxy group, 2-cyano-6-fluoro phenoxy group, 2-fluoro-6-methylsulfonyl phenoxy group, 2,6-difluoro-4-hydroxymethyl phenoxy group, 2,6-difluoro phenoxy group, 2-fluoromethyl-6-methylsulfonyl phenoxy group, 2-cyano-6-methylphenoxy group, 2-cyclopropylcarbonyl-6-fluoro phenoxy group, 3-fluoropyridin-2-yloxy group and the like are more preferred.

X denotes a nitrogen atom or CH.

For X and Y, preferably X is CH and Y is oxygen atom, or X is nitrogen atom and Y is sulfur atom.

R2 denotes a hydrogen atom or fluorine atom, but of these, hydrogen atom is preferred.

The "monocycle or bicyclic heteroaryl group" which A ring represents, among the heteroaryl group which the aforesaid R1 denotes, denotes monocyclic or bicyclic heteroaryl group represented by formula (II)



(II)

bonded at the 4 position of quinazoline or pyridopyrimidine skeleton in formula (I).

The said heteroaryl group may contain 1-3 heteroatoms, selected from the group comprising nitrogen atom, sulfur atom and oxygen atom, in each ring. Heteroaryl group of 5 or 6 membered monocycle is denoted or bicyclic heteroaryl group of 9-10 members is denoted.

As said A ring, as embodiments, for example, thiazolyl group, imidazolyl group, isothiazolyl group, thiadiazolyl group, triazolyl group, oxazolyl group, isoxazolyl group, pyrazinyl group, pyridyl group, pyridazinyl group, pyrazolyl group, pyrimidinyl group, thiazolo pyridyl group, thiazolo pyrazinyl group or benzothiazolyl group and the like are proposed. Among these, thiazolyl group, thiadiazolyl group, isoxazolyl group, pyrazinyl group, thiazolo pyridyl group, pyrazolyl group or pyridyl group are preferred, and thiazolo pyridyl group, thiadiazolyl group, pyrazinyl group or pyrazolyl group are more preferred.

Moreover, said A ring may have 1-3 the same or different substituents selected from the aforesaid substituent group β.

As "lower alkyl group" of said substituent, group same as in lower alkyl group of the said

definition is denoted, and for example methyl group, ethyl group, propyl group or isopropyl group and the like may be proposed.

As "lower alkoxy group" of said substituent, group same as in lower alkoxy group of the said definition is denoted, and for example methoxy group, ethoxy group, propoxy group, isopropoxy group and the like may be proposed.

As "halogen atom" of said substituent, group same as in halogen atom of the said definition is denoted, and for example fluorine atom, chlorine atom, bromine atom and the like may be proposed.

As "hydroxyalkyl group" of said substituent, group same as in hydroxyalkyl group of the said definition is denoted or denotes a substituted group wherein the hydrogen atom of hydroxy group in hydroxyalkyl group of the said definition is further substituted by lower alkyl group of the aforesaid definition, and for example hydroxymethyl group, hydroxyethyl group, methoxy methyl group, ethoxymethyl group and the like may be proposed.

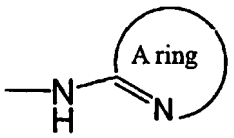
As "amino alkyl group" of said substituent, group same as in amino alkyl group of the said definition is denoted or denotes group wherein the amino group in amino alkyl group of the said definition is further substituted by lower alkyl group of the aforesaid definition, and for example aminomethyl group, 1-amino ethyl group, 2-amino ethyl group, methylamino ethyl group, dimethylaminoethyl group and the like may be proposed.

As "alkanoyl group" of said substituent, group same as in alkanoyl group of the said definition is denoted, and for example methyl carbonyl group, ethyl carbonyl group, propyl carbonyl group, isopropyl carbonyl group and the like may be proposed.

As "alkoxycarbonyl group" of said substituent, group wherein lower alkoxy group and carbonyl group of the said definition are combined is denoted, for example methoxycarbonyl group, ethoxycarbonyl group, isopropyl oxycarbonyl group, propyloxy carbonyl group and the like may be proposed.

In accordance with the above, as the group that may contain 1-3 substituents selected from

the substituent group β, and which represented by following formula (II-1)



(II-1)

as embodiments, for example, thiazolo [5,4-b] pyridin-2-ylamino group, 5-fluoro-thiazolo [5,4-b] pyridin-2-ylamino group, 5-methoxy-thiazolo [5,4-b] pyridin-2-ylamino group, thiazol-2-ylamino group, pyrazin-2-ylamino group, 3-methyl-[1,2,4] triazol-5-ylamino group, pyrimidin-4-ylamino group, 5-methyl-pyrazin-2-ylamino group, 5-chloropyrazin-2-ylamino group, 1-methyl-1H-pyrazol-3-ylamino group, 1-ethyl-1H-pyrazol-3-ylamino group, 5-methyl-1H-pyrazol-3-ylamino group, 1-(pyridin-2-yl)-1H-pyrazol-3-ylamino group, 1-(difluoromethyl)-1H-pyrazol-3-ylamino group, 1-methyl-1H-pyrazol-5-ylamino group, pyridin-2-ylamino group, 5-methylpyridin-2-ylamino group, 5-fluoropyridin-2-ylamino group, 5-chloro-thiazol-2-ylamino group, isoxazol-3-ylamino group, [1,2,4] thiadiazol-5-ylamino group, 3-methyl-[1,2,4] thiadiazol-5-ylamino group, 5-cyanopyridin-2-ylamino group, 4-methylthiazol-2-ylamino group, 4H-[1,2,4] triazol-3-ylamino group or pyridazin-3-ylamino group and the like are proposed. Among these, thiazolo [5,4-b] pyridin-2-ylamino group, 5-fluoro-thiazolo [5,4-b] pyridin-2-ylamino group, 5-methoxy-thiazolo [5,4-b] pyridin-2-ylamino group, pyrazin-2-ylamino group, 5-methyl-pyrazin-2-ylamino group, 5-chloropyrazin-2-ylamino group, 1-methyl-1H-pyrazol-3-ylamino group, 1-ethyl-1H-pyrazol-3-ylamino group, 5-methyl-1H-pyrazol-3-ylamino group, 1-(pyridin-2-yl)-1H-pyrazol-3-ylamino group, 1-(difluoromethyl)-1H-pyrazol-3-ylamino group, 1-methyl-1H-pyrazol-5-ylamino group, [1,2,4] thiadiazol-5-ylamino group or 3-methyl-[1,2,4] thiadiazol-5-ylamino group are preferred.

As compound shown with formula (I) in accordance with this invention, as embodiments, for example,

[6-(4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,

[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-thiazol-2-yl-amine,

[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-pyrazin-2-yl-amine,

(6-phenoxy quinazolin-4-yl)-pyrazin-2-yl-amine,

[6-(4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-pyrazin-2-yl-amine,

[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,

(6-phenoxy-quinazolin-4-yl)-thiazolo [5,4-b] pyridin-2-yl-amine,

[6-(2-fluoro-phenoxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,

[6-(1-methyl-1H-imidazol-2-yl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,

[6-(pyridin-2-yl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,

[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-(3-methyl-[1,2,4] thiadiazol-5-yl-amine,

[6-[pyrimidin-2-yl sulphanyl]-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,

[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,

[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-thiazolo [4,5-b] pyrazin-2-yl-amine,

Benzothiazol-2-yl-[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-amine,

[6-(3H-[1,2,3] triazol-4-yl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,

(1-methyl-1H-pyrazol-3-yl)-[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-amine,

[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-pyrimidin-4-yl-amine,

(5-methyl-pyrazin-2-yl)-[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-amine,

[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-pyridin-2-yl-amine,

(5-chloro-thiazol-2-yl)-[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-amine,

[6-(2-fluoro-1-fluoromethyl-ethoxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,

(6-isopropoxy-quinazolin-4-yl)-pyrazin-2-yl-amine,

(6-isopropoxy-quinazolin-4-yl)-thiazolo [5,4-b] pyridin-2-yl-amine,

[6-(2-hydroxy-(1S)-methyl-ethoxy-quinazolin-4-yl)]-thiazolo [5,4-b] pyridin-2-yl-amine,

(6-cyclopentyl oxy-quinazolin-4-yl)-thiazolo [5,4-b] pyridin-2-yl-amine,

[6-(2-fluoro-1-fluoromethyl-ethoxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,

[6-(2-fluoro-1-fluoromethyl-ethoxy)-quinazolin-4-yl]-isoxazol-3-yl-amine,

[6-(2-fluoro-1-fluoromethyl-ethoxy)-quinazolin-4-yl]-(5-fluoro-thiazolo [5,4-b] pyridin-2-yl)-amine,

[6-(2-fluoro-1-fluoromethyl-ethoxy)-quinazolin-4-yl]-(5-methoxy-thiazolo [5,4-b] pyridin-2-yl)-amine,

[6-(4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,

(6-phenoxy-pyrido [3,.2-d] pyrimidin-4-yl) thiazol-2-yl-amine,

[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-thiazol-2-yl-amine,

[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,

[6-(5-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,

Thiazolo [5,4-b] pyridin-2-yl-[6-(3H-[1,2,3] triazol-4-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-amine,

(6-methoxy-quinazolin-4-yl)-pyrazin-2-yl-amine,

(6-hydroxy-quinazolin-4-yl)-thiazolo [5,4-b] pyridin-2-yl-amine,

6-(1-methylpyrazol-3-yl sulphanyl)-thiazolo [5,4-b] pyridin-2-ylpyrido [3,2-d] pyrimidin-4-yl-amine,

(6-ethyl sulphanyl)-thiazolo [5,4-b] pyridin-2-yl pyrido [3,2-d] pyrimidin-4-yl-amine,

(5-methoxymethyl-1,2,4-triazol-3-yl sulphanyl) thiazolo [5,4-b] pyridin-2-yl pyrido [3,2-d] pyrimidin-4-yl-amine,

(5-methylpyrazin-2-yl)-6-(1,2,4-triazol-3-yl sulphanyl) pyrido [3,2-d] pyrimidin-4-yl-amine,

6-(1-methyl imidazol-2-yl sulphanyl)-(5-methylpyrazin-2-yl) pyrido [3,2-d] pyrimidin-4-yl-amine,

6-(imidazol-2-yl sulphanyl)-(5-methylpyrazin-2-yl) pyrido [3,2-d] pyrimidin-4-yl-amine,

6-(1-ethylimidazol-2-yl sulphanyl)-(5-methylpyrazin-2-yl) pyrido [3,2-d] pyrimidin-4-yl-amine,

(5-methylpyrazin-2-yl)-6-(1-methylpyrazol-3-yl sulphanyl) pyrido [3,2-d] pyrimidin-4-yl-amine,

6-(1,5-dimethylimidazol-2-yl sulphanyl)-(5-methylpyrazin-2-yl) pyrido [3,2-d] pyrimidin-4-yl-amine,

6-(4-methyl imidazol-2-yl sulphanyl)-(5-methylpyrazin-2-yl) pyrido [3,2-d] pyrimidin-4-yl-amine,

(5-methylpyridin-2-yl)-6-(1,2,4-triazole-3-yl sulphanyl) pyrido [3,2-d] pyrimidin-4-yl-amine,

(5-fluoropyridin-2-yl)-6-(1,2,4-triazol-3-yl sulphanyl) pyrido [3,2-d] pyrimidin-4-yl-amine,

[6-(pyridin-2-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,

[6-(1,3,4-thiadiazol-2-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,

[6-(1-methyl-1H-tetrazol-5-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,

[6-(4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-3-methyl-[1,2,4] thiadiazol-5-yl-amine,

[6-(4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]- (1-methyl-1H-pyrazol-3-yl)-amine,

[6-(3-fluoro-benzonitrile-2-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-3-methyl-[1,2,4] thiadiazol-5-yl-amine,

[6-(3H-[1,2,3] triazol-4-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]- (1-methyl-1H-pyrazol-3-yl)-amine,

[6-(5-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl] -(1-methyl-1H-pyrazol-3-yl)-amine,

[6-(3-chloro-pyridin-2-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]- (1-methyl-1H-pyrazol-3-yl)-amine,

[6-(3-cyano-pyridin-2-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]- (1-methyl-1H-pyrazol-3-yl)-amine,

[6-(3-amido-pyridin-2-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]- (1-methyl-1H-pyrazol-3-yl)-amine,

6-(1H-benzimidazol-2-yl sulphanyl)-N-(1-methyl-1H-pyrazol-3-yl) pyrido (3,2-d) pyrimidin-4-yl-amine,

6-[(5-amino-4H-1,2,4-triazol-3-yl) sulphanyl]-N-(1-methyl-1H-pyrazol-3-yl) pyrido (3,2-d) pyrimidin-4-yl-amine,

N-pyrazin-2-yl-6-(4H-1,2,4-triazol-3-yl sulphanyl) pyrido (3,2-d) pyrimidin-4-yl-amine,

N-isoxazol-3-yl-6-(4H-1,2,4-triazol-3-yl sulphanyl) pyrido (3,2-d) pyrimidin-4-yl-amine,

6-{[6-(4H-1,2,4-triazol-3-yl sulphanyl) pyrido [3,2-d] pyrimidin-4-yl] amino} nicotino nitrile,

(4-methyl-1,3-thiazol-2-yl)-6-(4-methyl-1,2,4-triazol-3-yl sulphanyl)-quinazolin-4-yl-amine,

(5-methyl-1,3-thiazol-2-yl)-6-(4-methyl-1,2,4-triazol-3-yl sulphanyl)-quinazolin-4-yl-amine,

6-(methyl benzoato-2-yl) sulphanyl-thiazolo [5,4-b] pyridin-2-yl quinazolin-4-yl-amine,

6-(2-hydroxymethyl phenyl sulphanyl)-thiazolo [5,4-b] pyridin-2-yl quinazolin-4-yl-amine,

6-(pyrazin-2-yl sulphanyl)-thiazolo [5,4-b] pyridin-2-yl quinazolin-4-yl-amine,

6-(3-fluoropyridin-2-yl sulphanyl)-thiazolo [5,4-b] pyridin-2-yl quinazolin-4-yl-amine,

6-(benzoato-2-yl sulphanyl)-thiazolo [5,4-b] pyridin-2-yl quinazolin-4-yl-amine,

6-(3-chloropyridin-2-yl sulphanyl)-(1-methylpyrazol-3-yl) quinazolin-4-yl-amine,

[6-(2-dimethylamino-ethyl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,

[6-(cyclopentyl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,

[6-(2-fluorophenyl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,

[6-(2-methoxyphenyl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,

[6-(3-chloropyridin-2-yloxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,

[6-(3-cyanopyridin-2-yloxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,

[6-(3-carboxamido pyridin-2-yloxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,

[6-(pyridin-2-yloxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,

[6-(3-methylpyridin-2-yloxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,

[6-(methylcarbamoyl-methyl oxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,

[6-(3-methylsulfonyl pyridin-2-yloxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,

[6-(3-chloropyridin-2-yloxy)-quinazolin-4-yl]-3-methyl-[1,2,4] thiadiazol-5-yl-amine,

[6-(3-fluoropyridin-2-yloxy)-quinazolin-4-yl]-3-methyl-[1,2,4] thiadiazol-5-yl-amine,

[6-(3-chloropyridin-2-yloxy)-quinazoline,-4-yl]-pyridin-2-yl-amine,

[6-(tetrahydro-2H-pyran-4-yloxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,

[6-(3,5-difluoro pyridin-2-yloxy)-quinazolin-4-yl]-3-methyl-[1,2,4] thiadiazol-5-yl-amine,

[6-(2-chloro-6- (methylsulfonyl) phenoxy)-quinazolin-4-yl]- (1-methyl-1H-pyrazol-3-yl)-amine,

[6-(2,4-difluoro phenoxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,

[6-(2-fluoro-6-(5-methyl-[1,2,4] oxadiazol-3-yl) phenoxy)-quinazolin-4-yl]-3 -methyl-[1,2,4] thiadiazol-5-yl-amine,

[6-(2-fluoro-4- (methylsulfonyl phenoxy)-quinazolin-4-yl]-3-methyl-[1,2,4] thiadiazol-5-yl-amine,

[6-(2-fluoro-6- (methylsulfonyl) phenoxy)-quinazolin-4-yl]- (1-methyl-1H-pyrazol-3-yl)-amine,

[6-(2-fluoro-6- (methylsulfonyl) phenoxy)-quinazolin-4-yl]-(1-ethyl-1H-pyrazol-3-yl)-amine,

[6-(2-fluoro-6- (methylsulfonyl) phenoxy)-quinazolin-4-yl]-pyrazin-2-yl-amine,

[6-(2-chloro-6- (methanesulphonyl amino) phenoxy)-quinazolin-4-yl]- (1-methyl-1H-pyrazol-3-yl)-amine,

3-fluoro-2-({4-[(pyrazin-2-yl) amino] quinazolin-6-yl} oxy) benzonitrile,

[6-(butyl lactone-2-yloxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,

[6-(2,4-difluoro-6- (methylsulfonyl) phenoxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,

[6-(2-fluoro-6- (methylsulfonyl) phenoxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,

N-(1-methyl-1H-pyrazol-3-yl)-6-[2-(methylsulfonyl) phenoxy] quinazolin-4-yl-amine,

3-fluoro-2-({4-[(5-methylpyrazin-2-yl) amino] quinazolin-6-yl) oxy) benzonitrile,

6-(3-chloropyridin-2-yl sulphanyl)-(1-methylpyrazol-3-yl) quinazolin-4-yl-amine,

6-(3-chloropyridin-2-yl sulphanyl)-(5-methyl-pyrazin-2-yl) quinazolin-4-yl-amine,

6-(3-chloropyridin-2-yl sulphanyl)-(1H-pyrazol-3-yl) quinazolin-4-yl-amine,

6-(acetyl piperidin-4-yl) oxy-N-[1,3] thiazolo [5,4-d] pyridin-2-yl quinazolin-4-yl-amine,

N-(1-methyl-1H-pyrazol-3-yl)-6- (pyrazin-2-yloxy) quinazolin-4-yl-amine,

N-(1-methyl-1H-pyrazol-3-yl)-6- (pyrimidin-4-yloxy) quinazolin-4-yl-amine,

6-[2-fluoro-1- (fluoromethyl) ethoxy]-N-[1,3] thiazolo [5,4-d] pyrimidin-2-yl quinazolin-4-yl-amine,

6-[(3-chloropyridin-2-yl) oxy]-N-1,3-thiazol-2-yl quinazolin-4-amine (1-methylpyrazol-3-yl) quinazolin-4-yl-amine,

6-(1,3-benzothiazol-2-yloxy)-N-(1-methyl-1H-pyrazol-3-yl) quinazolin-4-yl-amine,

N-(1-methyl-1H-pyrazol-3-yl)-6- (quinazolin-2-yloxy) quinazolin-4-yl-amine,

6-[(5-fluoropyridin-2-yl) oxy]-N-(1-methyl-1H-pyrazol-3-yl) quinazolin-4-yl-amine,

6-[(3-chloropyridin-2-yl) oxy]-N-(5-methyl-1H-pyrazol-3-yl) quinazolin-4-yl-amine,

N-(1-methyl-1H-pyrazol-3-yl)-6- (pyridin-3-yloxy) quinazolin-4-yl-amine,

6-[(3-chloropyridin-2-yl) oxy]-N-4H-[1,2,4]-triazol-3-yl quinazolin-4-yl-amine,

6-[(5-fluoropyridin-3-yl) oxy]-N-(1-methyl-1H-pyrazol-3-yl) quinazolin-4-yl-amine,

6-[(3-chloropyridin-2-yl) oxy]-N-[1,2,4]-thiadiazol-5-yl quinazolin-4-yl-amine,

N-(1-methyl-1H-pyrazol-3-yl)-6-[(3-methylpyridin-2-yl) oxy] quinazolin-4-yl-amine,
6-{[3-(difluoromethyl) pyridin-2-yl] oxy}-N-(1-methyl-1H-pyrazol-3-yl) quinazolin-4-yl-amine,
N-(1-methyl-1H-pyrazol-3-yl)-6-{[3-(trifluoromethyl) pyridin-2-yl] oxy} quinazolin-4-yl-amine,
[2-({4-[(1-methyl-1H-pyrazol-3-yl) amino] quinazolin-6-yl} oxy) pyridin-3-yl] methanol,
6-{[3-(fluoromethyl) pyridin-2-yl] oxy}-N-(1-methyl-1H-pyrazol-3-yl) quinazolin-4-yl-amine,
1-[2-({4-[(1-methyl-1H-pyrazol-3-yl) amino] quinazolin-6-yl} oxy) pyridine 3-yl] ethanone,
5-chloro-2-methyl-4-({4-[(1-methyl-1H-pyrazol-3-yl) amino] quinazolin-6-yl} oxy) pyridazin-3(2H)-one,
6-[(6-fluoropyridin-2-yl) oxy]-N-(1-methyl-1H-pyrazol-3-yl) quinazolin-4-yl-amine,
[3-fluoro-2-({4-[(1-methyl-1H-pyrazol-3-yl) amino] quinazolin-6-yl} oxy) phenyl] methanol,
6-[2-fluoro-6- (fluoromethyl) phenoxy]-N-(1-methyl-1H-pyrazol-3-yl) quinazolin-4-yl-amine,
[3-chloro-4-({4-[(1-methyl-1H-pyrazol-3-yl) amino] quinazolin-6-yl} oxy) phenyl] methanol,
Methyl-5- (methylsulfonyl)-2-({4-[(3-methyl-[1,2,4]-thiadiazol-5-yl) amino] quinazolin-6-yl} oxy) benzoate,
3-fluoro-2-({4-[(1-pyridin-2-yl-1H-pyrazol-3-yl) amino] quinazolin-6-yl} oxy) benzonitrile,
1-[3-fluoro-2-({4-[(1-methyl-1H-pyrazol-3-yl) amino] quinazolin-6-yl} oxy) phenyl] ethanone,
6-[(3-chloropyridin-2-yl) oxy]-N-[1-(difluoromethyl)-1H-pyrazol-3-yl] quinazolin-4-yl-amine,
3-chloro-N,N-dimethyl-2-({4-[(3-methyl-[1,2,4]-thiadiazol-5-yl) amino] quinazolin-6-yl} oxy) benzenesulphonamide,
6-[2-chloro-6- (ethylsulfonyl) phenoxy]-N-(3-methyl-1,2,4-thiadiazol-5-yl) quinazolin-4-yl-amine,
6-[2-fluoro-6- (methylsulfonyl) phenoxy]-N-(5-methylpyrazin-2-yl) quinazolin-4-yl-amine,
6-[2-chloro-6- (cyclopropyl sulfonyl) phenoxy]-N-(1-methyl-1H-pyrazol-3-yl) quinazolin-4-yl-amine,

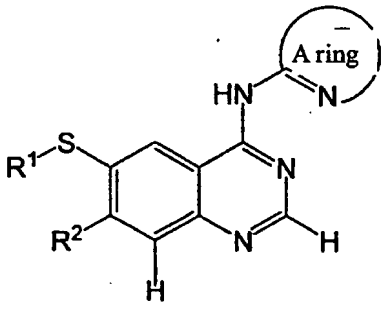
6-[2-fluoro-6- (methylsulfonyl) phenoxy]-N-1H-pyrazol-3-yl quinazolin-4-yl-amine,
6-[3-cyclopropyl pyridin-2-yl] oxy]-N-(1-methyl-1H-pyrazol-3-yl) quinazolin-4-yl-amine,
[2-({4-[(1-methyl-1H-pyrazol-3-yl) amino] quinazolin-6-yl} oxy)-3- (trifluoromethyl) phenyl] methanol,
6-[2-fluoro-6- (methylsulfonyl) phenoxy]-N-pyridazin-3-ylquinazolin-4-yl-amine,
N-(5-chloropyrazin-2-yl)-6-[2-fluoro-6- (methylsulfonyl) phenoxy] quinazolin-4-yl-amine,
[3,5-difluoro-4-({4-[(1-methyl-1H-pyrazol-3-yl)amino] quinazolin-6-yl} oxy) phenyl] methanol,
3-fluoro-2-({4-[(1-methyl-1H-pyrazol-5-yl) amino] quinazolin-6-yl} oxy) benzonitrile,
6-[4-methyl-2- (methylsulfonyl) phenoxy]-N-(1-methyl-1H-pyrazol-3-yl) quinazolin-4-yl-amine,
6-(2,6-difluoro phenoxy)-N-(1-methyl-pyrazol-3-yl) quinazolin-4-yl-amine,
1-[3-methyl-2-([4-[(1-methyl-pyrazol-3-yl) amino] quinazolin-6-yl] oxy) phenyl] ethanone,
6-[2-(fluoromethyl)-6- (methylsulfonyl) phenoxy]-N-(1-methyl-pyrazol-3-yl) quinazolin-4-yl-amine,
3-methyl-2-({4-[(1-methyl-pyrazol-3-yl) amino] quinazolin-6-yl} oxy) benzonitrile,
Cyclopropyl [3-fluoro-2-([4-[{1-methyl-pyrazol-3-yl} amino] quinazolin-6-yl] oxy) phenyl] methanone,
6-[2-fluoro-6- (methoxymethyl) phenoxy]-N-(1-methyl-pyrazol-3-yl) quinazolin-4-yl-amine,
[6-(5-chloro-3-fluoropyridin-2-yloxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
[6-(3-fluoropyridin-2-yloxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
6-[2-methyl-6- (methylsulfonyl) phenoxy]-N-(1-methyl-pyrazol-3-yl) quinazolin-4-yl-amine,
6-[2-(fluoromethyl)-6- (methylsulfonyl) phenoxy]-N-(1H-pyrazol-3-yl) quinazolin-4-yl-amine, or
[6-(2-fluoro-6- (methane sulfonamido) phenoxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine and the like may be proposed.
Among these, for example,
[6-(4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,
[6-(3H-[1,2,3] triazol-4-yl sulphanyl)-quinazolin-4-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,

[6-(2-fluoro-1-fluoromethyl-ethoxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,
[6-(2-hydroxy-(1S)-methyl-ethoxy-quinazolin-4-yl)]-thiazolo [5,4-b] pyridin-2-yl-amine,
[6-(4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,
(5-methylpyrazin-2-yl)-6-(1,2,4-triazol-3-yl sulphanyl) pyrido [3,2-d] pyrimidin-4-yl-amine,
(5-methylpyrazin-2-yl)-6-(1-methylpyrazol-3-yl sulphanyl) pyrido [3,2-d] pyrimidin-4-yl-amine,
[6-(4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
[6-(2-fluoro-6- (methylsulfonyl) phenoxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
[6-(2-fluoro-6- (methylsulfonyl) phenoxy)-quinazolin-4-yl]-(1-ethyl-1H-pyrazol-3-yl)-amine,
[6-(2-chloro-6- (methanesulphonyl amino) phenoxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
6-(3-chloropyridin-2-yl sulphanyl)-(1-methylpyrazol-3-yl) quinazolin-4-yl-amine,
6-(3-chloropyridin-2-yl) sulphanyl-(1H-pyrazol-3-yl) quinazolin-4-yl-amine,
5-chloro-2-methyl-4-({4-[(1-methyl-1H-pyrazol-3-yl) amino] quinazolin-6-yl} oxy) pyridazin-3(2H)-one,
6-[2-fluoro-6- (fluoromethyl) phenoxy]-N-(1-methyl-1H-pyrazol-3-yl) quinazolin-4-yl-amine,
1-[3-fluoro-2-({4-[[1-methyl-1H-pyrazol-3-yl] amino] quinazolin-6-yl) oxy) phenyl] ethanone,
6-[(3-chloropyridin-2-yl) oxy]-N-[1-(difluoromethyl)-1H-pyrazol-3-yl] quinazolin-4-yl-amine,
6-[2-chloro-6- (ethylsulfonyl) phenoxy]-N-(3-methyl-1,2,4-thiadiazol-5-yl) quinazolin-4-yl-amine,
6-[2-fluoro-6- (methylsulfonyl) phenoxy]-N-(5-methylpyrazin-2-yl) quinazolin-4-yl-amine,
6-[2-fluoro-6- (methylsulfonyl) phenoxy]-N-1H-pyrazol-3-yl quinazolin-4-yl-amine,
[3,5-difluoro-4-({4-[(1-methyl-1H-pyrazol-3-yl) amino] quinazolin-6-yl}oxy) phenyl] methanol,
6-(2,6-difluoro phenoxy)-N-(1-methyl-pyrazol-3-yl) quinazolin-4-yl-amine,

1-[3-methyl-2-([4-[(1-methyl-pyrazol-3-yl) amino] quinazolin-6-yl] oxy) phenyl] ethanone,
6-[2-(fluoromethyl)-6- (methylsulfonyl) phenoxy]-N-(1-methyl-pyrazol-3-yl) quinazolin-4-yl-amine,
3-methyl-2-({4-[(1-methyl-pyrazol-3-yl) amino] quinazolin-6-yl} oxy) benzonitrile,
Cyclopropyl [3-fluoro-2-([4-[{1-methyl-pyrazol-3-yl} amino] quinazolin-6-yl] oxy) phenyl] methanone,
[6-(3-fluoropyridin-2-yloxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
3-fluoro-2-({4-[(pyrazin-2-yl) amino] quinazolin-6-yl} oxy) benzonitrile,
6-[2-methyl-6- (methylsulfonyl) phenoxy]-N-(1-methyl-pyrazol-3-yl) quinazolin-4-yl-amine,
6-[2-(fluoromethyl)-6- (methylsulfonyl) phenoxy]-N-(1H-pyrazol-3-yl) quinazolin-4-yl-amine, or
[6-(2-fluoro-6- (methane sulfonamido) phenoxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine is preferred.

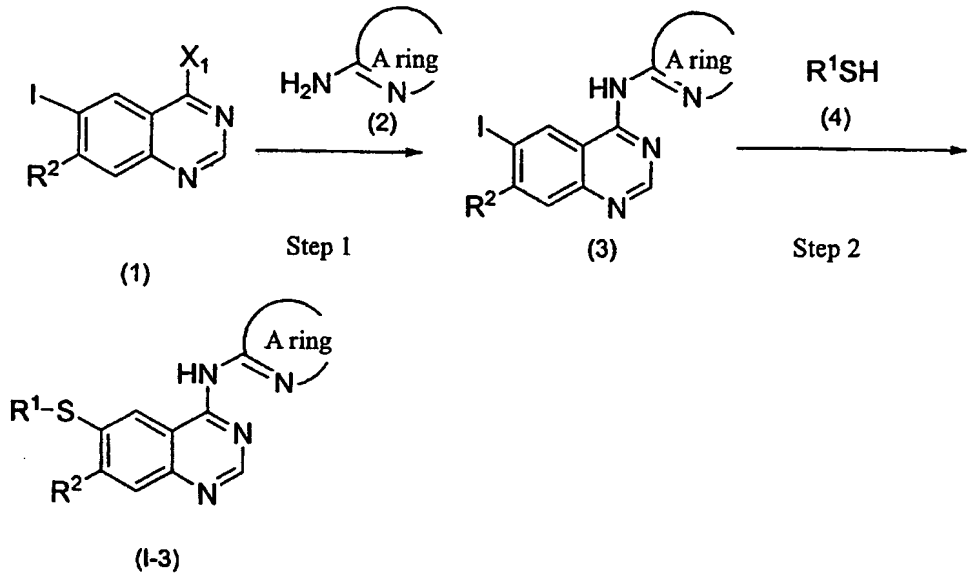
Moreover, any of the preferred embodiments of R1, R2, X, Y, A ring, substituent group α, substituent group β described above may combined.

Among compound in accordance with this invention, the compound represented by formula (I-3)



(I-3)

can for example be produced by the following process.



[wherein, X denotes a halogen atom, and the other symbols are the same as above].

(Step 1). This step is is process to produce compound (3) by reacting compound (1) and compound (2).

Preferably it is chlorine atom as X1 in compound (2).

Amount of compound (2) used in this step is usually 0-5-10 equivalents, more preferably 1-3 equivalents with respect to 1 equivalent of compound (1).

The reaction time is usually 0.1-24 hours, preferably 1-10 hours.

The reaction temperature is usually room temperature to boiling point of solvent temperature or 200 degrees, preferably 80-150 degrees.

As the reaction solvent used in this step, provided it does not hinder the reaction, it is not restricted in particular. However, as embodiments for example, phenol, toluene, xylene, N,N-dimethylformamide (hereinafter, abbreviated to DMF), N,N-dimethylacetamide (hereinafter, abbreviated to DMA), N-methylpyrrolidone (hereinafter, abbreviated to NMP), tetrahydrofuran (hereinafter, abbreviated to THF), dioxane, dimethoxyethane, ethanol,

isopropanol, butanol, methylene chloride, chloroform and the like are proposed. Wherein phenol, ethanol, isopropanol are preferred, and phenol is more preferred.

Compound (3) obtained in this way is isolated and purified by well known separation and refinement means, for example concentration, vacuum concentration, reprecipitation, solvent extraction, crystallization, chromatography and the like, or can be subjected to next step without being isolated and purified.

(Step 2). This step is process to produce compound(I-3) in accordance with this invention by reacting compound (3) and thiol compound (4) in the presence of base and copper salt.

As the copper salt used in this step, for example, copper iodide, copper bromide, copper chloride, copper oxide and the like may be proposed.

Amount of copper salt used in this step is usually 0.01-20 equivalents, preferably 0.1-3 equivalents, more preferably 0.2-1 equivalents, with respect to 1 equivalent of compound (3).

As the base used in this step, for example, tertiary aliphatic amine such as triethylamine, N,N-diisopropyl ethylamine, N,N-dimethylaniline, 1,8-diazabicyclo[5.4.0]undeca-7-ene (DBU), 1,5-azabicyclo[4.3.0] nona-5-ene (DBN) or the like, aromatic amine such as for example pyridine, 4-dimethylaminopyridine, picoline, lutidine, quinoline or isoquinoline and the like, alkali metal alkoxide such as for example potassium-tert butyrate, sodium ethylate or sodium methylate and the like, alkali metal hydroxide such as potassium hydroxide, sodium hydroxide and the like, alkali metal carbonate and the like such as potassium carbonate, sodium carbonate, cesium carbonate and the like are proposed. Wherein for example alkali metal carbonate and aromatic amine such as pyridine and the like are preferred, and in particular for example potassium carbonate, cesium carbonate, pyridine are more preferred.

Amount of base used in this step differs depending on amount of compound (3) used and kind of solvent, it is usually 0.5-10 equivalents, preferably 1-5 equivalents, more preferably 1-3 equivalents with respect to 1 equivalent of compound (3).

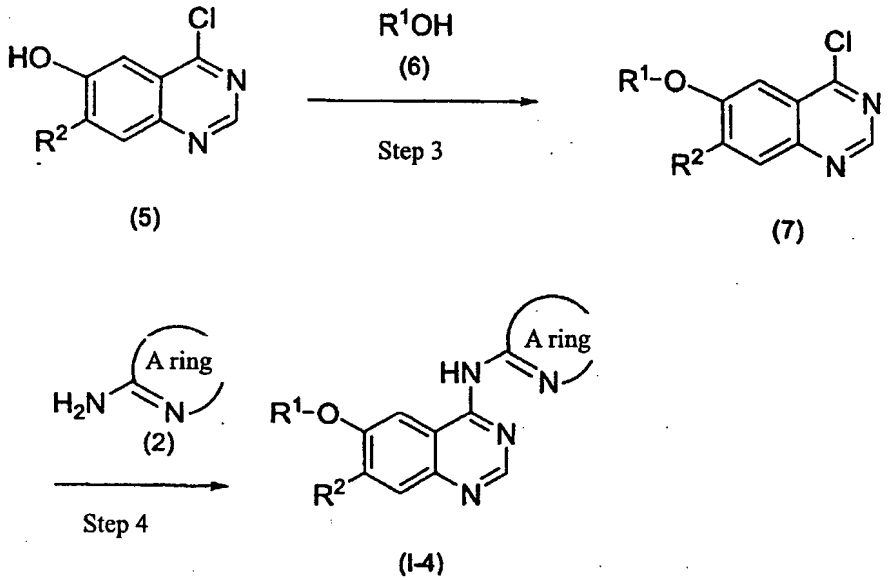
The reaction time is usually 0.1-50 hours, preferably 0.5-20 hours, more preferably 110 hours.

Reaction temperature is usually 50-200 degrees, preferably 80-170 degrees, more preferably 100-160 degrees.

Reaction solvent is not restricted in particular provided it does not hinder the reaction. However, for example, DMA, DMF, NMP, pyridine, quinoline, ethanol, isopropanol, dimethoxyethane and the like may be proposed. Among these, DMA, DMF, NMP, pyridine, quinoline are preferred, and DMA or DMF is more preferred.

Compound (I-3) in accordance with this invention obtained in this way can be isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallization, reprecipitation, chromatography and the like.

Moreover, for example, compound (I-4) in accordance with this invention can be produced using the following process.



[wherein, each symbol same as in the aforesaid definition].

(Step 3). This step is reaction to produce compound (7) by reacting compound (5) and compound (6). This reaction is so-called Mitsunobu reaction, and can be carried out in the presence of phosphine and azo compound by process in accordance with the liturature (for example Mitsunobu O, 'Use of diethyl azodicarboxylate and triphenylphosphine in synthesis and transformation of natural products', Synthesis, Vol 1, 1981, p 1-28), a process based on this, or a combination of these processes.

Amount of compound (6) used in this step is usually 0.5-10 equivalents, preferably 1-3 equivalents with respect to 1 equivalent of compound (5).

As the phosphine compound used in this step, usually for example triphenylphosphine, tributylphosphine and the like may be proposed.

The amount of phosphine compound used is usually 0.5-10 equivalents, preferably 1-3 equivalents for 1 equivalent of compound (5).

As the azo compound used, for example diethyl azodicarboxylate, diisopropyl azo dicarboxylate and the like may be proposed.

Amount of azo compound used is usually 0.5-10 equivalents, preferably 1-3 equivalents with respect to 1 equivalent of compound (5).

The reaction time is usually 1-48, preferably 4-12 hours.

The reaction temperature is usually 0 degrees to reflux temperature of reaction solvent, preferably 15 to 30 degrees.

The reaction solvent used in this step is not restricted in particular provided it does not hinder the reaction. However, as embodiments for example THF, toluene and the like may be proposed.

Compound (7) obtained in this way can be isolated and purified by well known separation and refinement means, for example concentration, vacuum concentration, reprecipitation,

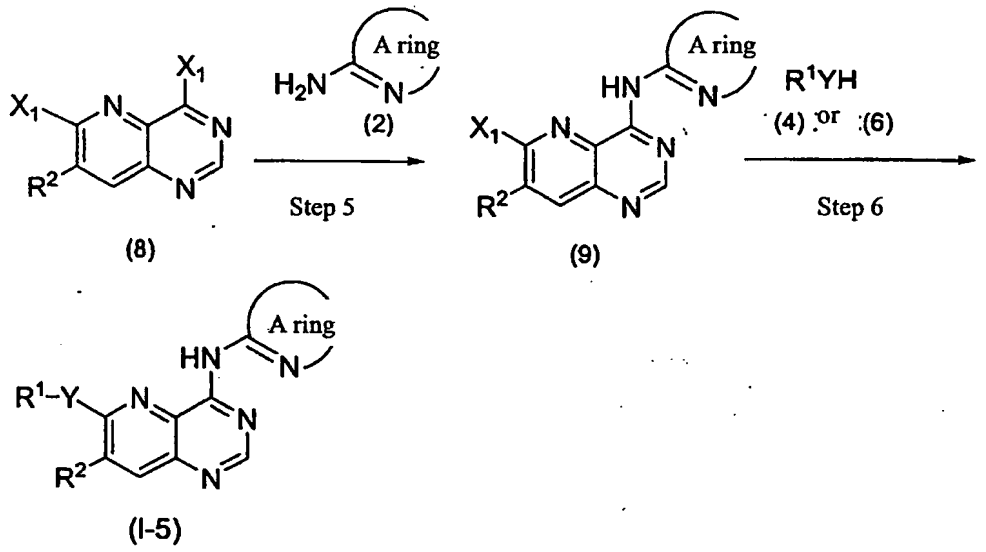
solvent extraction, crystallization, chromatography and the like.

(Step 4). This step is process to produce compound (I-4) in accordance with this invention by reacting compound (7) and the said compound (2).

Equivalent number of compound, the reaction temperature, reaction conditions such as reaction solvent or the like in this step are same as in the aforesaid step 1.

Compound (I-4) in accordance with this invention obtained in this way can be isolated and purified by well known separation and refinement means, for example concentration, vacuum concentration, reprecipitation, solvent extraction, crystallization, chromatography and the like.

Moreover, compound (I-5) in accordance with this invention can be produced for example by the following process.



[wherein, each symbol is the same as above].

(Step 5). This step is process to produce compound (9) by reacting compound (8) and the said compound (2).

As X1, chlorine atom is preferred.

In this reaction, reaction conditions such as the equivalent number of compounds, reaction temperature, reaction solvent or the like are same as in aforesaid step 1.

Compound (9) obtained in this way is isolated and purified by well known separation and refinement means, for example concentration, vacuum concentration, reprecipitation, solvent extraction, crystallization, chromatography and the like, or can be subjected to next step without isolating.

(Step 6). This step is process to produce compound-(I-5) in accordance with this invention by reacting compound (9) and compound (4) or (6) in the presence of base.

Amount of compound (4) or (6) used in this step is usually 0.2-10 equivalents, preferably 1-3 equivalents with respect to 1 equivalent of compound (9).

As the base used in this step, for example, tertiary aliphatic amine such as trimethylamine, triethylamine, N,N-diisopropyl ethylamine, N-methylmorpholine, N-methylpyrrolidine, N-methylpiperidine, N,N-dimethylaniline, 1,8-diazabicyclo[5.4.0] undeca-7-ene (DBU), 1,5-azabicyclo[4.3.0] nona-5-ene (DEN) or the like, aromatic amine such as pyridine, 4-dimethylaminopyridine, picoline, lutidine, quinoline or isoquinoline and the like, alkali metal such as metallic potassium, metallic sodium, metallic lithium and the like, alkali metal hydride such as sodium hydride, potassium hydride and the like, alkali metal alkyl compound such as butyllithium and the like, alkali metal alkoxide such as potassium-tert butylate, sodium ethylate or sodium methylate and the like, alkali metal hydroxide such as potassium hydroxide, sodium hydroxide and the like, alkali metal carbonate such as potassium carbonate, sodium carbonate, cesium carbonate and the like are proposed. Wherein for example tertiary aliphatic amine, alkali metal hydride, alkali metal carbonate or alkali metal alkoxide is preferred, and in particular for example triethylamine, N,N-diisopropyl ethylamine, 1,8-diazabicyclo[5.4.0] undeca-7-ene (DBU), sodium hydride or potassium carbonate, potassium-tert butylate, alkali metal alkoxide such as sodium ethylate or sodium methylate and the like are more preferred.

Amount of base used in this step is usually 0.2-10 equivalents, preferably 1-5 equivalents with respect to 1 equivalent of compound (9).

Reaction solvent used is not restricted in particular, provided it does not hinder the reaction. However, for example, inert solvent is preferred, and as embodiments for example, methylene chloride, chloroform, 1,2-dichloromethane, trichloroethane, DMF, DMA, NMP, acetone, ethanol, isopropanol, tert butanol, tert amyl alcohol, ethyl acetate, methyl acetate, acetonitrile, benzene, xylene, toluene, 1,4,-dioxane, THF, dimethoxyethane or a mixed solvent thereof is proposed. DMF, DMA, NMP, acetonitrile, isopropanol, tert amyl alcohol and the like are preferred, and DMF or DMA and the like is more preferred.

The reaction time is usually 0.2-100, preferably 1-40 hours.

Usually the reaction temperature is -20 degrees to temperature of boiling point of solvent, preferably 0 degrees to temperature of boiling point of solvent.

Compound (I-5) in accordance with this invention obtained in this way can be isolated and purified by well known separation and refinement means, for example concentration, vacuum concentration, reprecipitation, solvent extraction, crystallization, chromatography and the like.

Substituted quinazoline or pyridopyrimidine derivative put forward by this invention can be present as pharmacologically acceptable salt, and, the aforesaid salt can be produced in accordance with normal methods using a compound of the aforesaid (I-3) (I-4) or (I-5), which are included in compound (I) in accordance with this invention.

Compound in accordance with this invention can be made into the pharmacologically acceptable salt or ester by conventional procedures, and moreover conversely can be converted to free compound from salt or ester in accordance with normal methods.

As the aforesaid acid addition salt, the acid addition salt which is for example hydrohalic acid salt such as hydrochloride, hydrofluoride, hydrobromide, hydroiodide or the like,

inorganic acid salt such as nitrate, perchlorate, sulfate, phosphate, carbonate or the like; or organic acid salt , lower alkyl sulfonic acid salt such as methanesulfonate, trifluoromethanesulfonate, ethanesulfonate or the like, aryl sulfonic acid salt such as benzensulphonate, p-toluenesulfonate or the like, organic acid salt such as fumarate, succinate, citrate, tartrate, oxalate, maleate or the like, and organic acid such as amino acid or the like such as glutamate, aspartate or the like may be proposed.

Moreover, when the compound of this invention has acidic group in the said group, for example, a carboxyl group or the like, the aforesaid compound may be converted to the corresponding pharmacologically acceptable salt by treating with base. As the aforesaid base addition salt, for example, alkali metal salt such as sodium, potassium and the like, alkaline earth metal salt such as calcium, magnesium and the like, ammonium salt, organic base such as guanidine, triethylamine, dicyclohexylamine and the like, may be proposed.

Furthermore, the compound of this invention may be present as arbitrary hydrate or solvate of the free compound or salt thereof.

Moreover, conversely, in accordance with normal methods, conversion can be carried out to free compound from salt or ester, too.

Moreover, stereoisomer such as optical isomer, diastereoisomer, geometric isomer or the like, or tautomer, of the compound in accordance with this invention may exist, depending on its substituents. These isomers may all be said to be included in the compounds in accordance with this invention. Furthermore, arbitrary mixtures of these isomers may also be said to be included in compounds in accordance with this invention.

When the compound of this invention is used clinically, it may be formulated pharmaceutically with pharmacologically acceptable additive added to suit the form of administration. As additive in such cases, various additive usually used in pharmaceutical preparation sphere can be used, for example gelatin, lactose, refined sugar, titanium oxide, starch, crystalline cellulose, hydroxypropyl methyl cellulose, carboxymethylcellulose, maize starch, microcrystalline wax, white petrolatum, magnesium metasilicate aluminate, anhydrous calcium phosphate, citric acid, trisodium citrate, hydroxypropylcellulose,

sorbitol, sorbitan fatty acid ester, polysorbate, sucrose fatty acid ester, polyoxyethylene, hardened castor oil, polyvinylpyrrolidone, magnesium stearate, light anhydrous silicic acid, talc, vegetable oil, benzyl alcohol, gum arabic, propylene glycol, polyalkylene glycol, cyclodextrin, hydroxypropyl cyclodextrin and the like may be proposed.

A mixture of the compound of this invention and the aforesaid additive may be used as solid preparation (tablet, encapsulated formulation, granule, powder, suppository or the like) or liquid preparation (syrup, elixir agent, injection agent or the like). These preparations may be prepared according to ordinary process in pharmaceutical preparation sphere. Moreover, liquid preparation may be one which is dissolved or suspended in water or other suitable vehicle at the time of use. Moreover, particularly in the case of injection agent, it may be dissolved or suspended in physiological saline or glucose liquid in accordance with requirements, and moreover, a buffer agent and preservative may be added. These preparations may contain the compound of this invention in proportions of 1.0-100 wt.%, preferably 1.0-60 wt.%.

The pharmaceutical formulation of the compound of this invention can for example be carried out according to the following Preparation Example.

Preparation Example 1

10 pts. of compound of Example 1 described subsequently, heavy magnesia 15 pts. and lactose 75 pts. are uniformly mixed and are made into 350 micrometer or less powder or fine granulate. This powder is introduced into capsule container, and encapsulated formulation is formed.

Preparation Example 2

45 pts. of compound of later described Example 1, starch 15 pts, lactose 16 pts, crystalline cellulose 21 pts, polyvinyl alcohol 3 pts. and distilled water 30 pts are uniformly mixed, and thereafter, the mixture is pulverized, granulated, and dried, thereafter, the granules were classified and thereby granules having size of a diameter of 1410-177 μm are produced.

Preparation Example 3

Granules are produced by the same process as in Preparation Example 2, thereafter, calcium

stearate 3 pts. is added to this granule 96 pts., the mixture is compression-molded, and tablet of a diameter of 10 mm is produced.

Preparation Example 4

Crystalline cellulose 10 pts. and calcium stearate 3 pts. are added to 90 pts. of granules obtained by the process of Preparation Example 2, the mixture is compression-molded, and it is formed into tablet of a diameter of 8 mm. Thereafter, syrup gelatin, precipitated calcium carbonate mixed suspension is added to this, and sugar coated tablet is produced.

When the compound of this invention is used in clinical field, the dose and administration frequency thereof are different depending on the distinction of sex, age, body weight of the patient, severity of symptom, kind / range of target treatment effect or the like, however, in the case of oral administration, it is generally about 0.001-100mg/kg, preferably about 0.01-50mg/kg per day for an adult and is more preferably about 0.1-10 mg. There may be a case wherein the use of dose with the range beyond these limits is necessary.

As example of an appropriate quantity for oral administration, as single dosing or plurality of adminstrations of 2-4 times per day, it is from at least about 0.01 mg to at most 2.0 g. Preferably, the range of dose is from about 1.0 mg to about 200 mg by administration once or twice per day. More preferably, the range of dose is from about 10 mg to 100 mg by administration of once per day.

When intravenous administration or oral administration is used, a typical administration range is from about 0.001 mg about 100 mg with compound of formula (I) per 1 kg weight per day (preferably from 0.01 mg to about 10 mg) and more preferably it is from about 0.1 mg to 10 mg of compound of formula (I) per 1 kg weight per day.

As described earlier, the medicinal composition includes compound of formula (I) and pharmacologically acceptable carrier. The term "composition" includes a product formed by directly or indirectly combining, compounding or aggregating two or more arbitrary components, a product formed as a result of dissociation of one or more components, or a product formed as a result of other types of actions or interaction between components, as well as the active and inert component that consitute the acrrier (including pharmaceutically

acceptable excipient).

A composition which is formed by combination with pharmacologically permitted carrier and which contains compound of formula (I) in an effective dose for therapy, prevention or delay the onset of type II diabetes mellitus, is preferred.

When an effective dose of compound in accordance with this invention is administered to mammals, more particularly to human, any appropriate administration route can be used. For example, oral, rectum, local, vein, eye, lung, nose or the like can be used. As examples of administrative forms, there are tablet, troche, powder, suspension, solution, encapsulated formulation, cream, aerozol or the like, and tablet for oral administration is preferred.

When a composition for oral administration is prepared, any kind of vehicle usually used for ordinary drug can be used, and for example there are water, glycol, oil, alcohol, flavor additive, preservation charges, coloring agent or the like, and when a liquid composition for oral administration is prepared, for example, suspension, elixir agent and solution are proposed, and as carrier, for example, starch, sugar, microcrystalline cellulose, diluent, granulating agent, lubricant, binding agent, disintegrating agent or the like are proposed. When a solid body composition for oral administration is prepared, for example, powder, encapsulated formulation, tablet or the like are proposed, and among these, a solid body composition for oral administration is preferred.

From the ease of administration, tablet and encapsulated formulation are the most useful oral administration forms. The tablet can be coated using standard aqueous or non-aqueous technique in accordance with requirements.

In addition to the aforesaid ordinary administrative forms, the compound associating with formula (I) can be administered with release regulation means and/or delivery apparatus in accordance with for example U.S. patent number 3,845,770, 3,916,899, 3,536,809, 3,598,123, 3,630,200 and 4,008,719.

As medicinal composition in accordance with this invention suitable for oral administration, an encapsulated formulation containing pre-determined quantity of active component as

powder, or granule, or a water soluble liquid, water insoluble liquid, emulsion of water-in-oil type emulsion or oil-in-water type emulsion, cachet agent or tablet can be nominated. Such composition can be prepared using any kind of process in pharmaceutics, and all of the process includes a process in which the active component and a carrier comprising one or two or more necessary components are put together.

Generally, active ingredient and liquid carrier or well separated solid carrier or both are mixed thoroughly and uniformly, thereafter, composition is prepared by forming the product into suitable shape in accordance with requirements. For example, the tablet is in accordance with requirements prepared with 1 or more subspecies by compression and molding. Compression tablet is prepared by mixing in accordance with requirements mixed with binding agent, lubricant, inert excipient, detergent or dispersant, and by compressing the active component into arbitrary shape of powder, granules or the like. The formed tablet is prepared by molding a mixture wet powdery compound and inert liquid of diluent using a suitable machine.

Preferably each tablet includes active ingredient from about 1 mg to 1 g, and each cachet agent or encapsulated formulation includes active ingredient from about 1 mg to 500 mg.

Examples of administrative form of drug related to the compound of formula (I) are as follows.

Table 1

Suspension for injection (I. M.)

	mg/ml
Compound of formula (I)	10
Methyl cellulose	5.0
Tween 80	0.5
Benzyl alcohol	9.0
Benzalkonium chloride	1.0

Water used for injection is added, and the composition is made up to 1.0 ml.

Table 2

Tablet

	mg/tablet
Compound of formula (I)	25
Methyl cellulose	415
Tween 80	14.01
Benzyl alcohol	43.5
	Total 500 mg.

Table 3

Encapsulated formulation

	mg/capsule
Compound of formula (I)	25
Lactose powder	573.5
Magnesium stearate	1.5
	Total 600 mg.

Table 4

Aerozol

	per container
Compound of formula (I)	24 mg
Lecithin, NF Liq. Conc.	1.2 mg
Trichlorofluoromethane, NF	4.025 g
Dichlorodifluoromethane, NF	12.15 g

The compound of formula (I) can be used in combination with other agents used for therapy / prevention / delay of onset of type II diabetes mellitus in addition to the diseases or symptoms related to type II diabetes mellitus. The said other agents can be administered simultaneously to the compound of formula (I) or separately by usual administration route and the dose.

When the compound of formula (I) is used simultaneously with 1 or more agents, a medicinal composition including the compound of formula (I) and these other agents is

preferable. Accordingly, the medicinal composition in accordance with this invention also includes 1 or more active components in addition to the compound of formula (I). Examples of active components to be used in combination with the compound of formula (I) may not be limited to the followings, which may be administered separately or administered as the same medicinal composition.

(a) Other glucokinase activator,
(b) Biguanide (for example buformin, metformin, phenformin),
(c) PPAR agonist (for example troglitazone, pioglitazone, rosiglitazone),
(d) Insulin,
(e) Somatostatin,
(f) α-glucosidase inhibitor (for example Voglibose, miglitol, acarbose), and
(g) Insulin secretion accelerating agent (for example acetohexamide, carbutamide, chlorpropamide, glibournuride, gliclazide, glimerpiride, glipizide, gliquidone, glisoxepide, glyburide, glyhex amide, glypin amide, phenbut amide, tolaz amide, tolbut amide, tolcycl amide, nateglinide, repaglinide).

Weight ratio of compound of formula (I) with respect to the second active ingredient changes in a wide range, and moreover, it depends on the effective dose of each active ingredient. Accordingly for example, when PPAR agonist is used in combination with compound of formula (I), the weight ratio with respect to PPAR agonist of compound of formula (I) is generally about 1000:1 – 1:1000 and is preferably about 200:1 – 1:200. The combination of the compound of formula (I) and other active ingredient are in the said range. However, in each case, the effective dose of each active ingredient should be used.

Ordinary physician, veterinarian or clinician can easily determine the effective drug dose necessary to prevent, inhibit or arrest the progress of the disease.

Examples

Below this invention is further described in greater detail by reference to Examples. However, this invention is not restricted in any way by these Examples.

As silica gel column chromatography in Examples, Wakogel (Registered Trade Name) C-300 made by Wako Junyaku Co. or KP-Sil (Registered Trade Name) Silica prepacked column made by Biotage Co. was used. As the thin layer chromatography for separation, Kieselgel TM60F254, Art. 5744 made by Merck Corp. was used. As basic silica gel column chromatography, Chromatorex (Registered Trade Name) NH (100-250 mesh or 200-350 mesh) made by Fuji Sylisia Chemicals Co. was used.

Mass spectrum was measured with electro spray ionization method (ESI) or atmospheric pressure chemical ionization (APCI) using micromass ZQ made by Waters Co.

NMR spectrum was measured using Gemini-200 (200MHz; Varian), Gemini-300 (300MHz; Varian), Mercury 400 (400MHz; Varian) or Inova 400 (400MHz; Varian) type spectrometer, and as an internal standard, dimethylsulfoxide when measurement carried out with heavy dimethyl sulphoxide solution, and the total δ value was shown with ppm.

The meanings of abbreviation in Examples are shown below.

i-Bu: isobutyl group
n-Bu: n-butyl group
t-Bu: t-butyl group
Me: methyl group
Et: ethyl group
Ph: phenyl group
i-Pr: isopropyl group
n-Pr: n-propyl group
CDCl3: deuterated chloroform
CD3OD: deuterated methanol
DMSO-d6: heavy dimethyl sulphoxide

The meanings of abbreviation in nuclear magnetic resonance spectrum are shown below.

s: singlet

d: doublet

dd: double doublet

t: triplet

m: multiplet

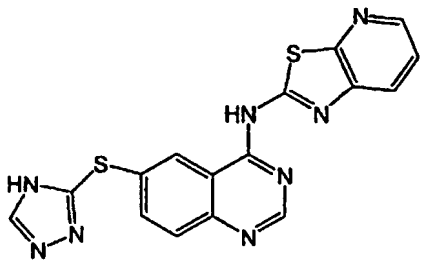
br: broad

q: quartet

J: coupling constant

Hz: hertz

Example 1



[6-(4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine

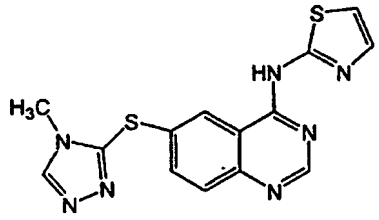
4-chloro-6-iodo-quinazoline 1.00 g (3.44 mmol) and thiazolo [5,4-b] pyridine-2-yl-amine 0.70 g (4.64 mmol) were heated with stirring in phenol (10 ml) at 135°C for four hours. Chloroform was added to the reaction liquor and washed with 1N-sodium hydroxide aqueous solution. The organic layer was dried and concentrated, and thereafter the obtained residue was purified using silica gel column chromatography (chloroform : methanol = 50 : 1) and (6-iodo-quinazolin-4-yl)-thiazolo [5,4-b] pyridine-2-yl-amine 486 mg (yield: 35 %) was obtained as a yellow solid.

Into N,N-dimethylacetamide solution (2 ml) of the obtained iodo body 80 mg (0.197 mmol) were added copper iodide 38 mg (0.197 mmol), cesium carbonate 128 mg (0.394 mmol) and 3-mercapto-1,2,4-triazole 30 mg (0.295 mmol), and thereafter the mixture was stirred at 140°C for five hours. Water was added to the reaction liquor, and extraction was carried out with chloroform. The organic layer was dried and concentrated, and thereafter the obtained residue was purified using thin layer silica gel chromatography (chloroform : methanol = 8 : 1) and the title compound 15 mg (yield: 20 %) was obtained as a yellow solid.

1H-NMR(COC13) δ: 7.43-7.46 (1H, m), 7.82 (1H, d, J = 8.8 Hz), 7.90 (1H, d, J = 8.8 Hz), 8.05 (1H, d, J = 8.0 Hz), 8.18 (1H, s), 8.31 (1H, s), 8.43 (1H, d, J = 3.6 Hz), 8.69 (1H, s).
ESI-MS (m/e): 379 (M+H)+.

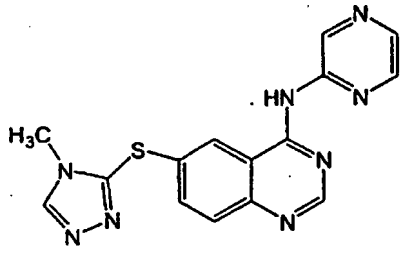
Using the same process as in aforesaid Example 1, compounds of Examples 2-21 were obtained. Below analysis data of these compounds is shown.

Example 2



[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-thiazol-2-yl-amine.
The compound of Example 2 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure, using 4-chloro-6-iodo-quinazoline, 2-amino-thiazole and 3-mercapto-4-methyl-1,2,4-triazole.
1H-NMR (CDCl3) δ : 3.66 (3H, s), 7.02 (1H, d, J = 3.6 Hz), 7.51 (1H, d, J = 3.6 Hz), 7.60-7.80 (2H, m), 8.00-8.35 (2H, m), 8.49 (1H, brs).
ESI-MS (m/e): 342 (M+H)+.

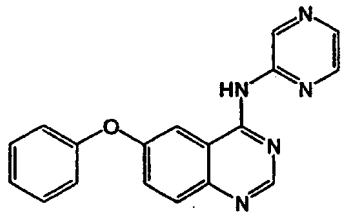
Example 3



[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-pyrazine-2-yl-amine.
The compound of Example 3 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure, using 4-chloro-6-iodo-quinazoline, 2-amino-pyrazine and 3-mercapto-4-methyl-1,2,4-triazole.

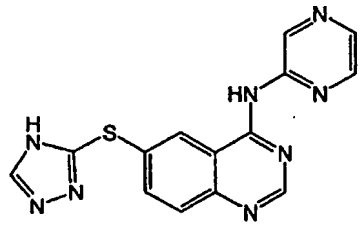
1H-NMR (CDCl3) δ : 3.68 (3Hx2/3, s), 3.70 (3Hx1/3, s), 7.38-7.70 (2Hx2/3, m), 7.77-7.98 (2Hx1/3, m), 8.03-8.62(4H, m), 8.62 (1Hx2/3, brs), 8.70 (1Hx2/3, brs), 8.99 (1Hx1/3, brs), 10.00 (1Hx1/3, brs).
ESI-MS (m/e): 337 (M+H)+.

Example 4



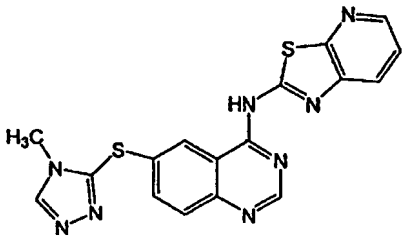
(6-phenoxy quinazolin-4-yl).-pyrazine-2-yl-amine
The compound of Example 4 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure, using 4-chloro-6-iodo-quinazoline, 2-amino-pyrazine and phenol.
1H-NMR (CDCl3) δ : 7.06-7.20 (2H, m), 7.35-7.52 (3H, m), 7.60-8.30 (5H, m), 8.37 (1Hx1/2, brs), 8.62 (1Hx1/2, brs), 8.89 (1Hx1/2, brs), 10.07 (1Hx1/2, brs).
ESI-MS (m/e): 316 (M+H) +.

Example 5



[6-(4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-pyrazine-2-yl-amine
The compound of Example 5 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure, using 4-chloro-6-iodo-quinazoline, 2-amino-pyrazine and 3-mercapto-1,2,4-triazole.
1H-NMR (CDCl3) δ : 7.85-7.98 (2H, m), 8.04-8.60 (4H, m), 8.63 (1Hx1/3, brs), 8.74 (1Hx1/3, brs), 8.85 (1Hx2/3, brs), 9.95 (1Hx2/3, brs).
ESI-MS (m/e): 323 (M+H)+.

Example 6



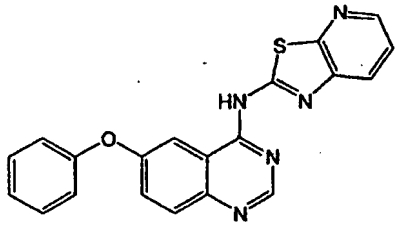
[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine

The compound of Example 6 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure, using 4-chloro-6-iodo-quinazoline, thiazolo [5,4-b] pyridine-2-yl-amine and 3-mercapto-4-methyl-1,2,4-triazole.

1H-NMR (CDCl3) δ : 3.72 (3H, s), 7.38 (1H, dd, J = 8.0, 4-4 Hz), 7.70-7.83 (3H, m), 7.98 (1H, d, J = 8.0 Hz), 8.35 (1H, s), 8.45 (1H, dd, J = 4.4, 1.6 Hz), 8.57 (1H, s).

ESI-MS (m/e): 393 (M+H)+.

Example 7



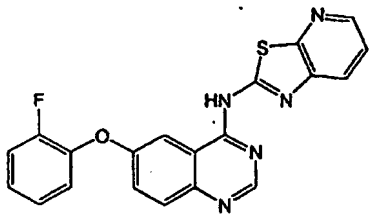
(6-phenoxy-quinazolin-4-yl).-thiazolo [5,4-b] pyridine-2-yl-amine

The compound of Example 7 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure, using 4-chloro-6-iodo-quinazoline, thiazolo [5,4-b] pyridine-2-yl-amine and phenol.

1H-NMR (CDCl3) δ : 7.07-7.27 (3H, m), 7.32-7.58 (4H, m), 7.77 (1H, d, J = 8.7 Hz), 7.99 (1H, dd, J = 8.1, 1.5 Hz), 8.13 (1H, d, J = 3.0 Hz), 8.23 (1H, s), 8.44 (1H, dd, J = 4.7, 1.5 Hz).

ESI-MS (m/e): 372 (M+H)+.

Example 8



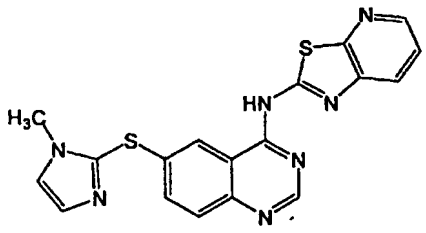
[6-(2-fluoro-phenoxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine

The compound of Example 8 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure, using 4-chloro-6-iodo-quinazoline, thiazolo [5,4-b] pyridine-2-yl-amine and 2-fluorophenol.

1H-NMR (CDCl3) δ : 7.19-7.77 (6H, m), 7.77 (1H, d, J = 9.0 Hz), 7.99 (1H, br-d, J = 7.5 Hz), 8.04 (1H, m), 8.22 (1H, s), 8.45 (1H, m).

ESI-MS (m/e): 390 (M+H)+.

Example 9



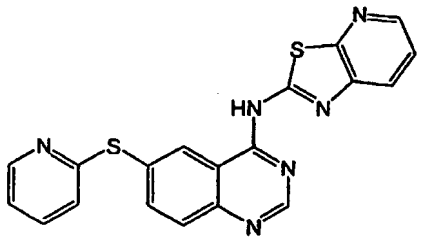
[6-(1-methyl-1H-imidazol-2-yl sulphanyl)-quinazoline-4 yl]-thiazolo [5,4-b] pyridine-2-yl-amine

The compound of Example 9 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure, using 4-chloro-6-iodo-quinazoline, thiazolo [5,4-b] pyridine-2-yl-amine and 2-mercapto-1-methyl-imidazole.

1H-NMR (CDCl3) δ : 3.74 (3H, s), 7.15 (1H, brs), 7.41 (1H, brs), 7.41 (1H, dd, J = 8.1, 4.8 Hz), 7.43-8.00 (3H, m), 8.03 (1H, dd, J = 8.1, 1.5 Hz), 8.40-8.52 (2H, m).

ESI-MS (m/e): 392 (M+H)+.

Example 10



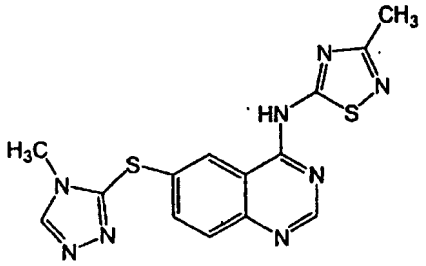
[6-(pyridin-2-yl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine

The compound of Example 10 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure, using 4-chloro-6-iodo-quinazoline, thiazolo [5,4-b] pyridine-2-yl-amine and 2-mercaptopyridine.

1H-NMR (CDCl3) δ : 7.04-7.16 (2H, m), 7.39 (1H, dd, J = 8.1, 4.8 Hz), 7.64 (1H, m), 7.78 (1H, br-d, J = 8.7), 7.90-8.04 (2H, m), 8.29 (1H, brs), 8.41-8.52 (2H, m), 8.33 (1H, brs).

ESI-MS (m/e): 389 (M+H)+.

Example 11



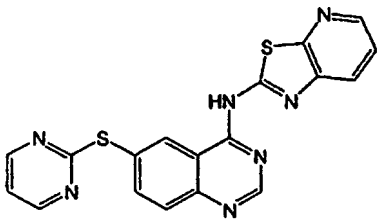
[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-(3-methyl-[1,2,4] thiadiazol-5-yl-amine)

The compound of Example 11 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure, using 4-chloro-6-iodo-quinazoline, 5-amino-2-methyl-1,2,4-thiadiazole and 3-mercapto-4-methyl-1,2,4-triazole.

1H-NMR(CDCl3) δ 2.59 (3H, s), 3.73 (3H, s), 7.87 (1H, d, J = 8.8 Hz), 7.95 (1H, d, J = 8.8 Hz), 8.37 (1H, s), 8.55 (1H, s), 8.97 (1H, s).

ESI-MS (m/e): 357 (M+H)+.

Example 12



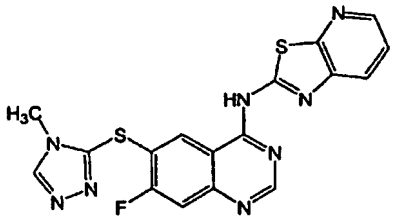
[6-(pyrimidin-2-yl sulphanyl)-quinazolin-4-yl]-thiazolo [514-b] pyridine-2-yl-amine

The compound of Example 12 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure, using 4-chloro-6-iodo-quinazoline, thiazolo [5,4-b] pyridine-2-yl-amine and 2-mercaptopyrimidine.

1H-NMR (CDCl3) δ : 7.07 (1H, t, J = 4.8), 7.39 (1H, dd, J = 8.1, 4.8 Hz), 7.80-8.12 (3H, m), 8.40-8.60 (4H, m), 8.78 (1H, m).

ESI-MS (m/e): 390 (M+H) +.

Example 13



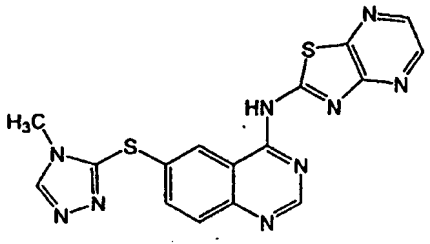
[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazoline-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine

The compound of Example 13 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure, using 4-chloro-7-fluoro-6-iodo-quinazoline, thiazolo [5,4-b] pyridine-2-yl-amine and 3-mercapto-4-methyl 1,2,4-triazole.

1H-NMR (CDCl3) δ : 3.82 (3H, s), 7.41 (1H, dd, J = 8.1, 4.8 Hz), 7.59 (1H, br-d, J = 11.1 Hz), 7.98 (1H, br-d, J = 8.1 Hz), 8.37 (1H, s), 8.46 (1H, br-d, J = 4.8 Hz), 8.60-8.90 (2H, m).

ESI-MS (m/e): 411 (M+H) +.

Example 14



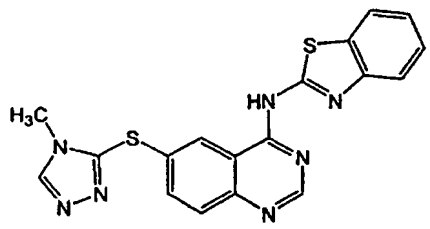
[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-thiazolo [4,5-b] pyrazine-2-yl-amine

The compound of Example 14 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure, using 4-chloro-6-iodo-quinazoline, thiazolo [5,4-b] pyrazine-2-yl-amine and 3-mercapto-4-methyl 1,2,4-triazole.

1H-NMR (CDCl3) δ : 3.72 (3H, s), 7.74-7.81 (2H, m), 8.26 (1H, d, J = 2.8 Hz), 8.37 (1H, d, J = 2.8 Hz), 8.49 (1H, s), 8.62 (1H, d, J = 1.6 Hz), 8.77 (1H, s).

ESI-MS (m/e): 394 (M+H)+.

Example 15



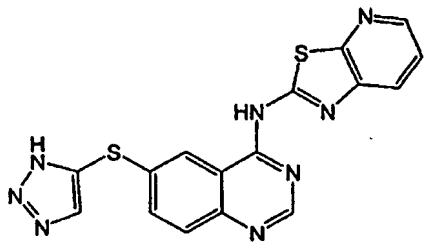
Benzthiazol-2-yl-[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-amine

The compound of Example 15 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure, using 4-chloro-6-iodo-quinazoline, 2-amino-benzothiazole and 3-mercapto-4-methyl 1,2,4-triazole.

1H-NMR(CDCl3) δ 3.68 (3H, s), 7.32 (1H, m), 7.45 (1H, m), 7.67-7.72 (2H, m), 7.79-7.81 (2H, m), 8.31-8.34 (2H, m), 8.60 (1H, s).

ESI-MS (m/e): 392 (M+H)+.

Example 16



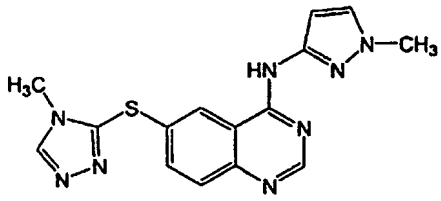
[6-(3H-[1,2,3] triazol-4-yl sulphanyl)-quinazoline-4-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine

The compound of Example 16 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure, using 4-chloro-6-iodo-quinazoline, thiazolo [5,4-b] pyridine-2-yl-amine and 3H-[1,2,3] triazole-4-thiol.

1H-NMR (CDCl3) δ : 7.43 (1H, dd, J = 8.1, 4.8 Hz), 7.65-7.86 (2H, m), 7.88 (1H, s), 8.03 (1H, dd, J = 8.1, 1.5 Hz), 8.39-8.60 (3H, m).

ESI-MS (m/e): 379 (M+H)+.

Example 17



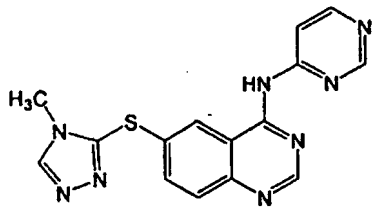
(1-methyl-1H-pyrazol-3-yl)-[6-(4-methyl-4H-[112,4] triazol-3-yl sulphanyl)-quinazolin-4-yl] one amine

The compound of Example 17 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure, using 4-chloro-6-iodo-quinazoline, 3-amino-1-methyl-1H-[1,2] pyrazole and 3-mercapto-4-methyl 1,2,4-triazole.

1H-NMR(CDCl3) δ 3.74(3H, s), 3.91 (3H, s), 6.88 (1H, d, J = 2.4 Hz), 7.42 (1H, d, J = 2.4 Hz), 7.89 (1H, dd, J = 2.0, 8.4 Hz), 8.03 (1H, d, J = 8.4 Hz), 8.36 (1H, s), 8.56 (1H, d, J = 2.0 Hz), 8.78 (1H, s).

ESI-MS (m/e): 339 (M+H)+.

Example 18



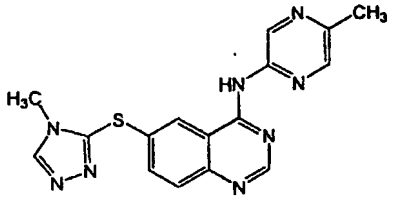
[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-pyrimidine-4-yl-amine

The compound of Example 18 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure, using 4-chloro-6-iodo-quinazoline, 4-aminopyrimidine and 3-mercapto-4-methyl 1,2,4-triazole.

1H-NMR(CDCI9) δ : 3.82 (3H, s), 7.45 (1H, m), 7.59-7.63 (2H, m), 7.95 (1H, dd, J = 8.8, 1.6 Hz), 7.69 (1H, d, J = 8.0 Hz), 7.92 (1H, brs), 8.07 (1H, d, J = 8.8 Hz), 8.45 (1H, s), 8.50 (1H, d, J = 1.6 Hz), 8.87 (1H, s).

ESI-MS (m/e): 336 (M+H)+.

Example 19



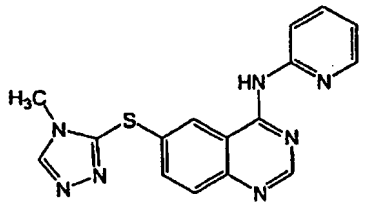
(5-methyl-pyrazine-2-yl)-[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-amine

The compound of Example 19 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure, using 4-chloro-6-iodo-quinazoline, 2-amino-5-methylpyrazine and 3-mercapto-4-methyl 1,2,4-triazole.

1H-NMR(CD3OD) δ : 2.61 (3H, s), 3.78 (3H, s), 7.87 (1H, d, J = 8.8 Hz), 7.95 (1H, dd, J = 8.8, 2.0 Hz), 8.44 (1H, brs), 8.70 (1H, s), 8.74 (1H, d, J = 2.0 Hz), 8.83 (1H, s), 9.35 (1H, s).

ESI-MS (m/e): 351 (M+H)+.

Example 20



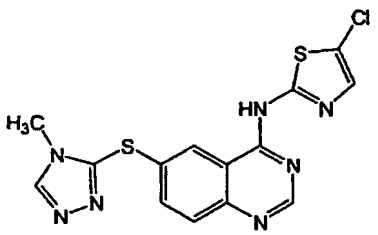
[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-pyridine-2-yl-amine

The compound of Example 20 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure, using 4-chloro-6-iodo-quinazoline, 2-aminopyridine and 3-mercapto-4-methyl 1,2,4-triazole.

1H-NMR(CDCl3) δ 3.76 (3H, s), 7.33 (1H, m), 7.85-7.95 (2H, m), 8.12 (1H, m), 8.26-8.37 (2H, m), 8.42 (1H, s), 8.63 (1H, s), 8.83 (1H, s).

ESI-MS (m/e): 336 (M+H)+.

Example 21



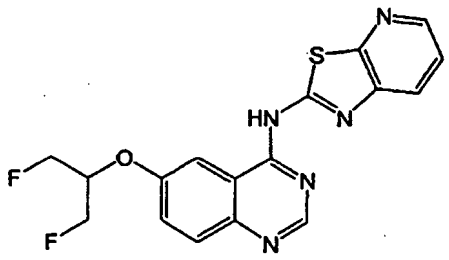
(5-chloro-thiazol-2-yl)-[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-amine

The compound of Example 21 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure, using 4-chloro-6-iodo-quinazoline, 2-amino-5-chloro thiazole and 3-mercapto-4-methyl 1,2,4-triazole.

1H-NMR(CD3OD) δ : 3.72 (3H, s), 7.35 (1H, s), 7.70-7.78 (2H, m), 8.48 (1H, s), 8.53 (1H, d, J = 1.6 Hz), 8.68 (1H, s).

ESI-MS (m/e): 376 (M+H)+.

Example 22



[6-(2-fluoro-1-fluoromethyl-ethoxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine

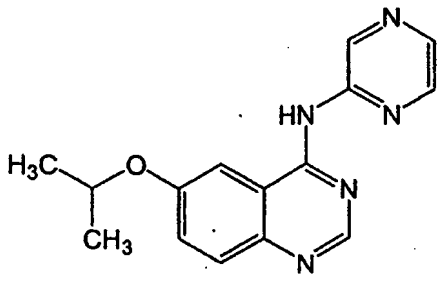
4-chloro-6-hydroxy-quinazoline 500 mg (2.78 mmol), 1,3-difluoro-2-propanol 800 mg (8.33 mmol) and triphenylphosphine 2.18 g (8.33 mmol) were dissolved in THF 30 ml, and diethylazo dicarboxylate 3.62 g (8.33 mmol) was added at room temperature. The reaction liquor was stirred at room temperature for further three hours, and thereafter, saturated aqueous sodium bicarbonate solution was added, and extraction was carried out with chloroform. The organic layer was dried and concentrated, and thereafter the obtained residue was purified using silica gel column chromatography (hexane : ethyl acetate = 1 : 2) and 4-chloro-6-(2-fluoro-1-fluoromethyl-ethoxy)-quinazoline 530 mg (yield: 74 %) was obtained as a yellow solid.

The obtained chloro body 38 mg (0.147 mmol) and thiazolo [5,4-b] pyridine-2-yl-amine 22 mg (0.147 mmol) were heated with stirring in phenol (0.2 ml) at 140°C for two hours. Chloroform was added to the reaction liquor and the reaction liquior was washed with 1N-sodium hydroxide aqueous solution. The organic layer was dried and concentrated, and thereafter the obtained residue was purified using thin layer silica gel chromatography (chloroform : methanol = 10 : 1) and the title compound 15 mg (yield: 27 %) was obtained as a yellow solid.

1H-NMR (CDCl3) δ : 4.70-4.73 (2H, m), 4.84-4.86 (2H, m), 4.90-5.02 (2H, m), 7.36 (1H, dd, J = 8.0, 4.4 Hz), 7.49 (1H, dd, J = 8.8, 2.8 Hz), 7.74 (1H, d, J = 8.8 Hz), 7.98 (1H, dd, J = 8.0, 1.6 Hz), 8.04 (1H, d, J = 2.8 Hz), 8.22 (1H, s), 8.45 (1H, dd, J = 4.4,.1.2 Hz).

ESI-MS (m/e): 374 (M+H)+.

Example 23



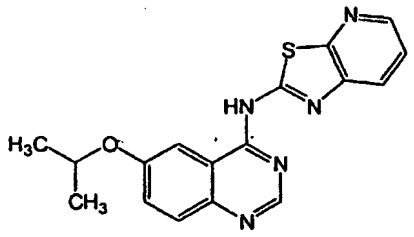
(6-isopropoxy-quinazolin-4-yl)-pyrazine-2-yl-amine

The compound of Example 23 was produced by the same process as in Example 22, a process based on this or a combination of these and a normal procedure, using 4-chloro-6-hydroxy-quinazoline, 2-propanol and 2-aminopyrazine.

1H-NMR (CDCl3) δ : 1.43 (6H, d, J = 6.0 Hz), 4.70-4.90 (1H, m), 7.19-7.68 (2H, m), 7.89-8.08 (1Hx3/2, m), 8.18-8.40 (2H, m), 8.71 (1Hx1/2, brs), 8.83 (1Hx1/2, brs), 10.10 (1Hx1/2, brs).

ESI-MS (m/e): 282 (M+H)+.

Example 24



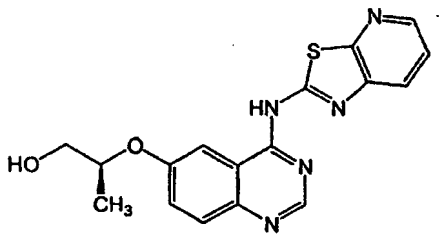
(6-isopropoxy-quinazolin-4-yl)-thiazolo [5,4-b] pyridine-2-yl-amine

The compound of Example 24 was produced by the same process as in Example 22, a process based on this or a combination of these and a normal procedure, using 4-chloro-6-hydroxy-quinazoline, 2-propanol and thiazolo [5,4-b] pyridine-2-yl-amine.

1H-NMR (CDCl3) δ : 1.43 (6H, d, J = 6.0 Hz), 4.85 (1H, brs), 7.34 (1H, dd, J = 8.4, 4.0 Hz), 7.38 (1H, d, J = 8.0 Hz), 7.71 (1H, brs), 7.90 (1H, brs), 7.95 (1H, dd, J = 8.0, 1.2 Hz), 8.20 (1H, brs), 8.43 (1H, d, J = 4.0 Hz).

ESI-MS (m/e): 338 (M+H)+.

Example 25



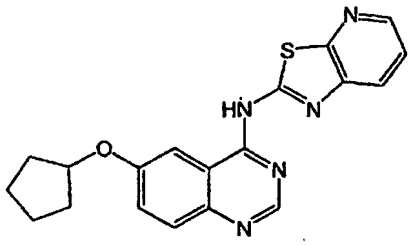
[6-(2-hydroxy-(1S)-methyl-ethoxy-quinazolin-4-yl)]-thiazolo [5,4-b] pyridine-2-yl-amine

The compound of Example 25 was produced by the same process as in Example 22, a process based on this or a combination of these and a normal procedure, using 4-chloro-6-hydroxy-quinazoline, (2S)-1-(tert-butyldimethylsilyloxy)-2-propanol and thiazolo [5,4-b] pyridine-2-yl-amine.

1H-NMR (DMSO) δ : 1.35 (3H, d, J = 6.0 Hz), 3.61-3.67 (2H, m), 4.75 (1H, m), 7.61 (1H, dd, J = 8.0, 4.8 Hz), 7.76 (1H, dd, J = 8.8, 2.4 Hz), 8.04 (1H, d, J = 8.8 Hz), 8.14 (1H, dd, J = 8.0, 1.6 Hz), 8.19 (1H, d, J = 2.4 Hz), 8.58 (1H, dd, J = 4.8, 1.6 Hz), 9.27 (1H, s).

ESI-MS (m/e): 354 (M+H)+.

Example 26



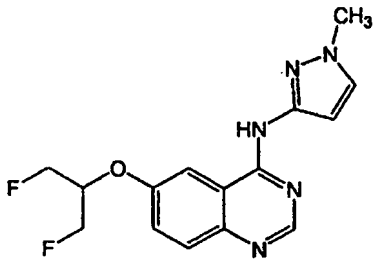
(6-cyclopentyl oxy-quinazolin-4-yl)-thiazolo [5,4-b] pyridine-2-yl-amine

The compound of Example 26 was produced by the same process as in Example 22, a process based on this or a combination of these and a normal procedure, using 4-chloro-6-hydroxy-quinazoline, cyclopentanol and thiazolo [5,4-b] pyridine-2-yl-amine.

1H-NMR (CDCl3) δ : 1.69-2.05 (8H, m), 5.00 (1H, m), 7.34 (1H, dd, J = 8.0, 6.4 Hz), 7.37 (1H, brs), 7.69 (1H, d, J = 8.0 Hz), 7.92 (1H, brs), 7.94 (1H, d, J = 8.0 Hz), 8.17 (1H, brs), 8.43 (1H, brs).

ESI-MS (m/e): 364 (M+H)+.

Example 27



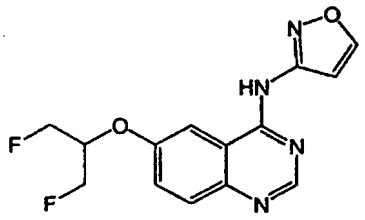
[6-(2-fluoro-1-fluoromethyl-ethoxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine

The compound of Example 27 was produced by the same process as in Example 22, a process based on this or a combination of these and a normal procedure, using 4-chloro-6-hydroxy-quinazoline, 1,3-difluoro-2-propanol and 3-amino-1-methyl-1H-[1,2] pyrazole.

1H-NMR (CDCl3) δ : 3.86 (3H, s), 4.60-4.70 (2H, m), 4.74-4.85 (2H, m), 4.90 (1H, m), 7.00 (1H, d, J = 2.4 Hz), 7.38 (1H, d, J = 2.4 Hz), 7.49 (1H, dd, J = 8.8, 2.4 Hz), 7.61 (1H, d, J = 2.4 Hz), 7.83 (1H, d, J = 8.8 Hz), 8.66 (1H, s).

ESI-MS (m/e): 307 (M+H)+.

Example 28



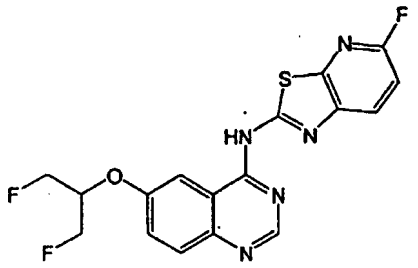
[6-(2-fluoro-1-fluoromethyl-ethoxy)-quinazolin-4-yl]-isoxazol-3-yl-amine

The compound of Example 28 was produced by the same process as in Example 22, a process based on this or a combination of these and a normal procedure, using 4-chloro-6-hydroxy-quinazoline, 1,3-difluoro-2-propanol and 3-aminoisoxazole.

1H-NMR(CD3OD) δ : 4.72-4.84 (2H, m), 4.85-4.88 (2H, m), 5.05 (1H, m), 7.35 (1H, s), 7.58 (1H, d, J = 8.8 Hz), 7.85 (1H, d, J = 8-8 Hz), 7.94 (1H, s), 8.45 (1H, s), 8.69 (1H, s).

ESI-MS (m/e): 307 (M+H)+.

Example 29



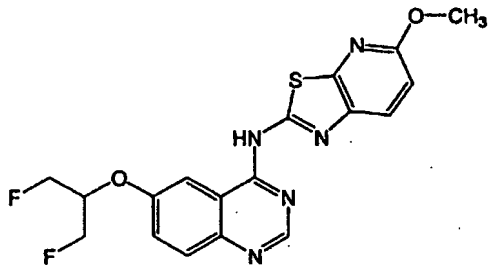
[6-(2-fluoro-1-fluoromethyl-ethoxy)-quinazolin-4-yl]-(5-fluoro-thiazolo [5,4-b] pyridine-2-yl)-amine

The compound of Example 29 was produced by the same process as in Example 22, a process based on this or a combination of these and a normal procedure, using 4-chloro-6-hydroxy-quinazoline, 1,3-difluoro-2-propanol and 5-fluoro-thiazolo [5,4-b] pyridine-2-yl-amine.

1H-NMR(CD3OD) δ : 4.71-4.73 (2H, m), 4.83-4.85 (2H, m), 5.00 (1H, m), 7.00 (1H, dd, J = 8.8, 1.6 Hz), 7.47 (1H, dd, J = 8.8, 2.8 Hz), 7.73 (1H, d, J = 8.8 Hz), 8.01 (1H, d, J = 2.8 Hz), 8.04 (1H, dd, J = 8.8, 1.6 Hz), 8.20 (1H, s).

ESI-MS (m/e): 392 (M+H)+.

Example 30

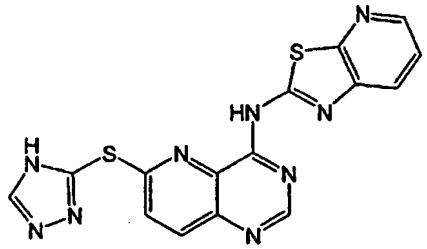


[6-(2-fluoro-1-fluoromethyl-ethoxy)-quinazolin-4-yl]-(5-methoxy-thiazolo [5,4-b] pyridine-2-yl)-amine

The compound of Example 29 was produced by the same process as in Example 22, a process based on this or a combination of these and a normal procedure, using 4-chloro-6-hydroxy-quinazoline, 1,3-difluoro-2-propanol and 5-methoxy-thiazolo [5,4-b] pyridine.

1H-NMR(CD3OD) δ : 4.04 (3H, s), 4.70-4.75 (2H, m), 4.80-4.86 (2H, m), 5.08 (1H, m), 6.94 (1H, d, J = 8.4 Hz), 7.70 (1H, d, J = 8.4 Hz), 7.78-7.91 (2H, m), 8.12 (1H, d, J = 2.8 Hz), 8.80 (1H, s).
ESI-MS (m/e): 404. (M+H)+.

Example 31

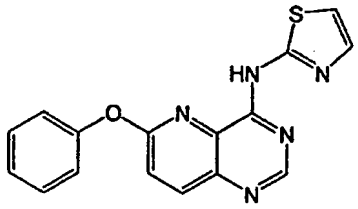


6-(4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine

4,6-dichloro-pyrido [3,2-d] pyrimidine 100 mg (0.503 mmol) and thiazolo [5,4-b] pyridine-2-yl-amine 76 mg (0.503 mmol) were heated with stirring in phenol (0.3 ml) at 140°C for two hours. Ethyl acetate was added to the reaction liquor, and furthermore the formed solid was purified using thin layer silica gel column chromatography (chloroform : methanol = 10 : 1), and (6-chloro-pyrido [3-2-d] pyrimidine-4-yl)-thiazolo [5,4-b] pyridine-2-yl-amine 78 mg (yield: 45 %) was obtained as a yellow solid.

Into N,N-dimethylacetamide solution (1 ml) of the obtained chloro body 25 mg (0.080 mmol) were added DBU 18 mg (0.120 mmol) and 3-mercapto-1,2,4-triazole 12 mg (0.120 mmol) and thereafter, the mixture was stirred at 140°C for 3 hours. The reaction liquor was concentrated under reduced pressure and thereafter the obtained residue was refined using reverse phase separation HPLC (0.1 % TFA-containing water : acetonitrile = 90 : 10 to 10 : 90), and the title compound 4 mg (yield: 13 %) was obtained as a yellow solid.
1H-NMR(CD3OD) δ : 7.70 (1H, dd, J = 8.0, 4.8 Hz), 7.81 (1H, d, J = 8.4 Hz), 8.26 (1H, d, J = 8.4 Hz), 8.35 (1H, dd, J = 8.0, 1.6 Hz), 8.61-8.63 (2H, m), 9.07 (1H, s).
ESI-MS (m/e): 380 (M+H)+.

Example 32



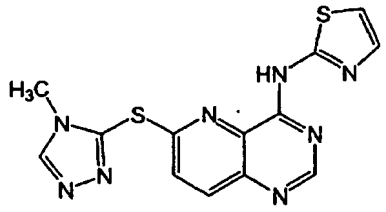
(6-phenoxy-pyrido [3,2-d] pyrimidine-4-yl)-thiazol-2-yl-amine

The compound of Example 32 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure, using 4,6-dichloro-pyrido [3,2-d] pyrimidine, 2-aminothiazole and phenol.

1H-NMR(CDCl3) δ : 7.04 (1H, d, J = 3.6 Hz), 7.23 (2H, d, J = 8.4 Hz), 7.33 (1H, t, J = 7.2 Hz), 7.48-7.52 (3H, m), 8.24 (1H, d, J = 8.8 Hz), 8.88 (1H, s), 9.53 (1H, s).

ESI-MS (m/e): 322 (M+H)+.

Example 33



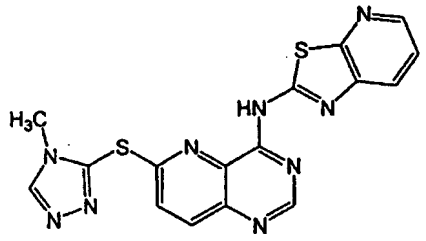
[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-thiazol-2-yl-amine

The compound of Example 33 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure, using 4,6-dichloro-pyrido [3,2-d] pyrimidine, 2-aminothiazole and 3-mercapto-4-methyl-1,2,4-triazole.

1H-NMR (CDCl3) δ : 3.82 (3H, s), 7.12 (1H, d, J = 3.6 Hz), 7.53 (1H, d, J = 3.6 Hz), 7.63 (1H, d, J = 8.8 Hz), 8.14 (1H, d, J = 8.8 Hz), 8.63 (1H, s), 8.89 (1H, s).

ESI-MS (m/e): 343 (M+H)+.

Example 34



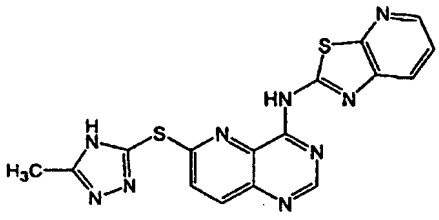
[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine

The compound of Example 34 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure, using 4,6-dichloro-pyrido [3,2-d] pyrimidine, thiazolo [5,4-b] pyridine-2-yl-amine and 3-mercapto-4-methyl-1,2,4-triazole.

1H-NMR(CD3OD) δ : 3.85 (3H, s), 7.47 (1H, m), 7.68 (1H, d, J = 8.8 Hz), 8.09 (1H, m), 8.20 (1H, d, J = 8.8 Hz), 8.46 (1H, brs), 8.74 (1H, brs), 8.95 (1H, brs).

ESI-MS (m/e): 394 (M+H)+.

Example 35



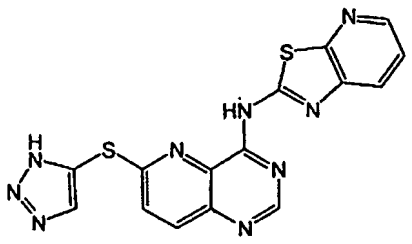
[6-(5-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine

The compound of Example 35 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using 4,6-dichloro-pyrido [3,2-d] pyrimidine, thiazolo [5,4-b] pyridine-2-yl-amine and 3-mercapto-5-methyl-1,2,4-triazole.

1H-NMR(CD3OD) δ : 3.85 (3H, s), 7.47 (1H, m), 7.68 (1H, d, J = 8.8 Hz), 8.09 (1H, m), 8.20 (1H, d, J = 8.8 Hz), 8.46 (1H, brs), 8.74 (1H, brs), 8.95 (1H, brs).

ESI-MS (m/e): 394 (M+H)+.

Example 36



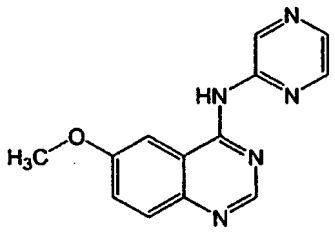
Thiazolo [5,4-b pyridine-2-yl-[6-(3H-[1,2,3] triazol-4-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-amine

The compound of Example 36 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using 4,6-dichloro-pyrido [3,2-d] pyrimidine, thiazolo [5,4-b] pyridine-2-yl-amine and 3H-[1,2,3] triazole-4-thiol.

1H-NMR (CDCl3) δ : 7.42 (1H, brs), 7.50 (1H, brs), 8.03-8.06 (2H, m), 8.13 (1H, d, J = 8.4 Hz), 8.48 (1H, brs), 8.90 (1H, s).

ESI-MS (m/e): 380 (M+H)+.

Example 37



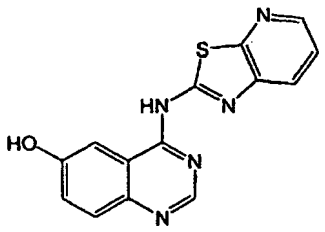
(6-methoxy-quinazolin-4-yl)-pyrazine-2-yl-amine

The compound of Example 37 was produced by the process used for production of (6-iodo-quinazolin-4-yl)-thiazolo [5,4-b] pyridine-2-yl-amine in Example 1, a process based on this or a combination of these and a normal procedure, using 4-chloro-6-methoxy-quinazoline and 2-aminopyrazine.

1H-NMR (CDCl3) δ : 3.99 (3Hx1/2, s), 4.01 (3Hx1/2, s), 7.14-8.35 (5H, m), 8.39 (1Hx1/2, brs), 8.72 (1Hx1/2, brs), 8.85 (1Hx1/2, brs), 10.10 (1Hx1/2, brs).

ESI-MS (m/e): 255 (M+H)+.

Example 38



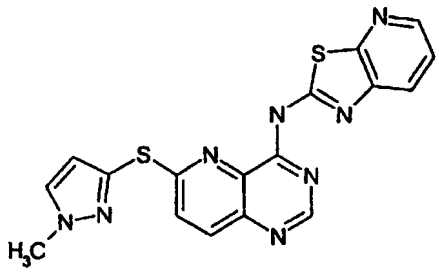
(6-hydroxy-quinazolin-4-yl)-thiazolo [5,4-b] pyridine-2-yl-amine

The compound of Example 38 was produced by the process used for production of (6-iodo-quinazolin-4-yl)-thiazolo [5,4-b] pyridine-2-yl-amine in Example 1, a process based on this or a combination of these and a normal procedure, using 6-acetoxy-4-chloro-quinazoline and thiazolo [5,4-b] pyridine-2-yl-amine.

1H-NMR (DMSO) δ : 7.49-7.53 (2H, m), 7.77 (1H, brs), 7.98 (1H, brs), 8.07 (1H, brs), 8.45 (1H, d, J = 3.6 Hz), 10.31 (1H, s).

ESI-MS (m/e): 296 (M+H)+.

Example 39



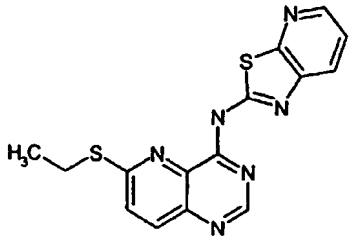
6-(1-methylpyrazol-3-yl sulphanyl)-thiazolo [5,4-b] pyridin-2-yl pyrido [3,2-d) pyrimidine-4-yl-amine

The compound of Example 39 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using 3-mercapto-1-methylpyrazole, thiazolo [5,4-b] pyridine-2-yl-amine and 4,6-dichloro-pyrido [3,2-d] pyrimidine.

1H-NMR(CD3OD) δ : 4.09 (3H, s), 6.67 (1H, d, J = 2.0 Hz), 7.49 (1H, dd, J = 8.0, 4.8 Hz), 7.53 (1H, d, J = 8.8 Hz), 7.76 (1H, d, J = 2.0 Hz), 8.06 (1H, d, J = 8.8 Hz), 8.13 (1H, dd, J = 8.0, 1.6 Hz), 8.47 (1H, dd, J = 4-8,1.6 Hz), 8.92 (1H, s).

ESI-MS (m/e): 393 (M+H)+.

Example 40



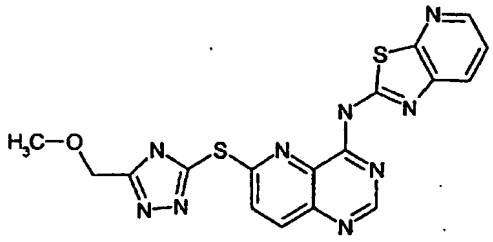
(6-ethyl sulphanyl)-thiazolo [5,4-b] pyridin-2-yl pyrido [3,2-d] pyrimidine-4-yl-amine

The compound of Example 40 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using ethanethiol, 4,6-dichloro-pyrido [3,2-d] pyrimidine and thiazolo [5,4-b] pyridine-2-yl-amine.

1H-NMR (CDCl3) δ : 1.53 (3H, t, J = 7.2 Hz), 3.40 (2H, q, J = 7.2 Hz), 7.41 (1H, dd, J = 8.0, 4.8 Hz), 7.61 (1H, d, J = 8.8 Hz), 8.02 (1H, d, J = 8.8 Hz), 8.05 (1H, dd, J = 8.0, 1.6 Hz), 8.51 (1H, dd, J = 4.8, 1.6 Hz), 8.95 (1H, s).

ESI-MS (m/e): 341 (M+H)+.

Example 41



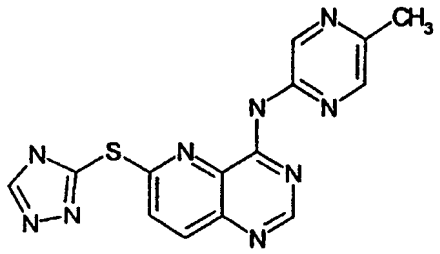
(5-methoxymethyl-1,2,4-triazol-3-yl sulphanyl)-thiazolo [5,4-b] pyridin-2-yl pyrido [3,2-d] pyrimidine-4-yl-amine

The compound of Example 41 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using 3-mercapto-5-methoxymethyl [1,2,4] triazole, 4,6-dichloro-pyrido [3,2-d] pyrimidine and thiazolo [5,4-b] pyridine-2-yl-amine.

1H-NMR(CD3OD). δ : 3.55 (3H, s), 4.75 (2H, s), 7.49 (1H, dd, J = 8.0-4.8 Hz), 7.73 (1H, d, J = 8.8 Hz), 8.10 (1H, d, J = 8.0 Hz), 8.14 (1H, d, J = 8.8 Hz), 8.48 (1H, d, J = 4.8 Hz), 8.96 (1H, s).

ESI-MS (m/e): 424 (M+H)+.

Example 42



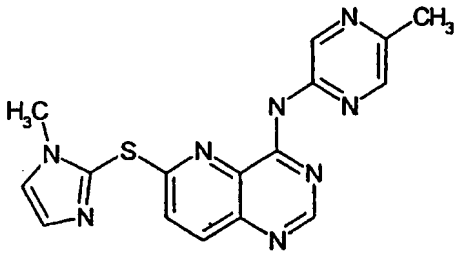
(5-methylpyrazine-2-yl)-6-(1,2,4-triazol-3-yl sulphanyl) pyrido [3,2-d] pyrimidine-4-yl-amine

The compound of Example 42 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using 3-mercapto-[1,2,4] triazole, 4,6-dichloro-pyrido [3,2-d] pyrimidine and 2-amino-5-methyl-pyrazine.

1H-NMR(CD3OD) δ : 2.60 (3H, s), 7.64 (1H, d, J = 9.20 Hz), 8.06 (1H, d, J = 9.20 Hz), 8.23 (1H, s), 8.52 (1H, s), 8.80 (1H, s), 9.88 (1H, d, J = 1-6 Hz).

ESI-MS (m/e): 338 (M+H)+.

Example 43



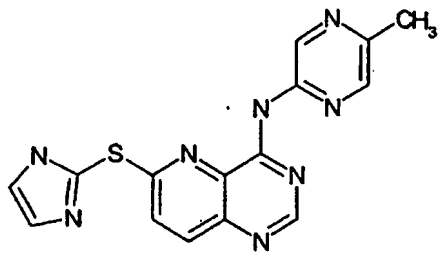
6-(1-methyl imidazol-2-yl sulphanyl)-(5-methylpyrazine-2-yl) pyrido [3,2-d] pyrimidine-4-yl-amine

The compound of Example 43 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using 2-mercapto-1-methyl imidazole, 2-amino-5-methylpyrazine and 4,6-dichloro-pyrido [3,2-d] pyrimidine.

1H-NMR(CD3OD) δ : 2.60 (3H, s), 3.82 (3H, s), 7.34 (1H, d, J = 1.2 Hz), 7.39-7.43 (2H, m), 8.07 (1H, d, J = 8.8 Hz), 8.29 (1H, s), 8.80 (1H, s), 9.85 (1H, d, J = 1.2 Hz).

ESI-MS (m/e): 351 (M+H)+.

Example 44



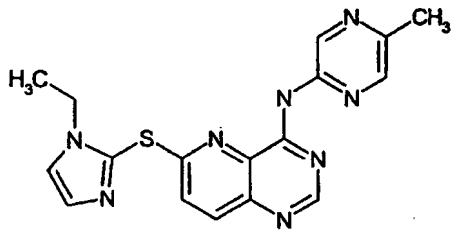
6-(imidazol-2-yl sulphanyl)-(5-methylpyrazine-2-yl) pyrido [3,2-d] pyrimidine-4-yl-amine

The compound of Example 44 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using 2-mercaptoimidazole, 2-amino-5-methylpyrazine and 4,6-dichloro-pyrido [3,2-d] pyrimidine.

1H-NMR(CD3OD) δ : 2.59 (3H, s), 7.32 (1H, d, J = 8.8 Hz), 7.35 (2H, s), 8.00 (1H, d, J = 8.8 Hz), 8.27 (1H, d, J = 1.2 Hz), 8.76 (1H, s), 9.83 (1H, d, J = 1.2 Hz).

ESI-MS (m/e): 337 (M+H)+.

Example 45



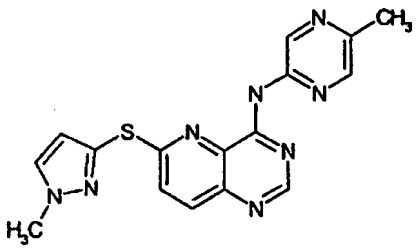
6-(1-ethylimidazol-2-yl sulphanyl)-(5-methylpyrazine-2-yl) pyrido [3,2-d] pyrimidine-4-yl-amine.

The compound of Example 45 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using 1-ethyl-2-mercaptoimidazole, 2-amino-5-methyl-pyrazine and 4,6-dichloro-pyrido [3,2-d] pyrimidine.

1H-NMR(CD3OD) δ : 1.42 (3H, t, J = 7.2 Hz), 2.59 (3H, s), 4.21 (2H, q, J = 7.2 Hz), 7.37 (1H, s), 7.49 (1H, d, J = 8.8 Hz), 7.54 (1H, d, J = 1.2 Hz), 8.10 (1H, d, J = 8.8 Hz), 8.33 (1H, s), 8.80 (1H, s), 9.83 (1H, d, J = 1.2 Hz).

ESI-MS (m/e): 365 (M+H)+.

Example 46



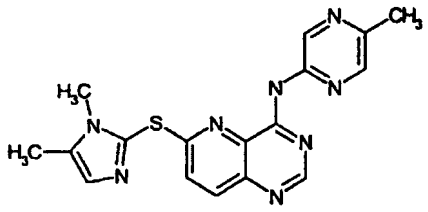
(5-methylpyrazine-2-yl)-6-(1-methylpyrazol-3-yl sulphanyl) pyrido [3,2-d] pyrimidine-4-yl-amine

The compound of Example 46 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using 3-mercapto-1-methylpyrazole, 2-amino-5-methylpyrazine and 4,6-dichloro-pyrido [3,2-d] pyrimidine.

1H-NMR(CD3OD) δ : 2.59 (3H, s), 4.08 (3H, s), 6.66 (1H, d, J = 2.0 Hz), 7.55 (1H, d, J = 8.8 Hz), 7.80 (1H, d, J = 2.0 Hz), 8.00 (1H, d, J = 8.8 Hz), 8.33 (1H, s), 8.77 (1H, s), 9.85 (1H, d, J = 1.2 Hz).

ESI-MS (m/e): 351 (M+H)+.

Example 47



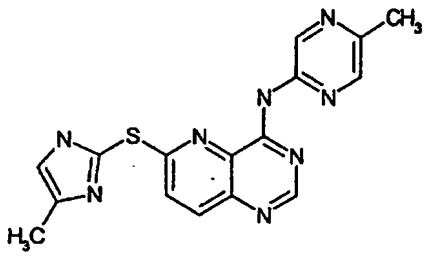
6-(1,5-dimethylimidazol-2-yl sulphanyl)-(5-methylpyrazine-2-yl) pyrido [3,2-d] pyrimidine-4-yl-amine

The compound of Example 47 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using 2-mercapto-1,5-dimethylimidazole, 2-amino-5-methylpyrazine and 4,6-dichloro-pyrido [3,2-d] pyrimidine.

1H-NMR(CD3OD) δ : 2.44 (3H, s), 2.60 (3H, s), 3.70 (3H, s), 7.10 (1H, s), 7.48 (1H, d, J = 8.8 Hz), 8.08 (1H, d, J = 8.8 Hz), 8.31 (1H, s), 8.80 (1H, s), 9.84 (1H, d, J = 1.2 Hz).

ESI-MS (m/e): 365 (M+H)+.

Example 48



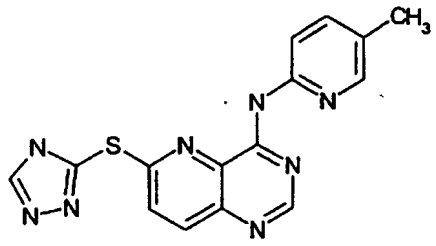
6-(4-methyl imidazol-2-yl sulphanyl)-(5-methylpyrazine-2-yl) pyrido [3,2-d] pyrimidine-4-yl-amine.

The compound of Example 48 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using 2-mercapto-4-methyl imidazole, 2-amino-5-methylpyrazine and 4,6-dichloro-pyrido [3,2-d] pyrimidine.

1H-NMR(CD3OD) δ : 2.37 (3H, s), 2.59 (3H, s), 7.04 (1H, s), 7.37 (1H, d, J = 8.8 Hz), 8.00 (1H, d, J = 8.8 Hz), 8.29 (1H, s), 8.76 (1H, s), 9.83 (1H, d, J = 1.2 Hz).

ESI-MS (m/e): 351 (M+H)+.

Example 49



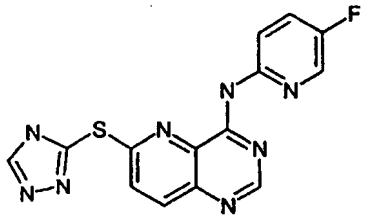
(5-methylpyridine-2-yl)-6-(1,2,4-triazol-3-yl sulphanyl) pyrido [3,2-d] pyrimidine-4-yl-amine

The compound of Example 49 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using 3-mercapto-[1,2,4] triazole, 2-amino-5-methylpyrazine and 4,6-dichloro-pyrido [3,2-d] pyrimidine.

1H-NMR(CD3OD) δ : 2.28 (3H, s), 7.53 (1H, d, J = 8.8 Hz), 7.57 (1H, dd, J = 8.8, 3.2 Hz), 7.93 (1H, d, J = 8.8 Hz), 8.08 (1H, s), 8.33 (1H, s), 8.54 (1H, d, J = 8.8 Hz), 8.65 (1H, s).

ESI-MS (m/e): 337 (M+H)+.

Example 50



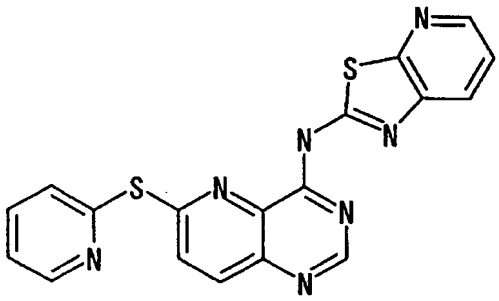
(5-fluoropyridine-2-yl)-6-(1,2,4-triazol-3-yl sulphanyl) pyrido [3,2-d] pyrimidine-4-yl-amine

The compound of Example 50 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using 3-mercapto-[1,2,4] triazole, 2-amino-5-fluoropyridine and 4,6-dichloro-pyrido [3,2-d] pyrimidine.

1H-NMR(CD3OD) δ : 7.51-7.60 (2H, m), 7.63 (1H, d, J = 8.8 Hz), 8.04 (1H, d, J = 8.8 Hz), 8.24 (1H, d, J = 2.4 Hz), 8.75 (1H, s), 8.77-8.81 (1H, m).

ESI-MS (m/e): 341 (M+H)+.

Example 51



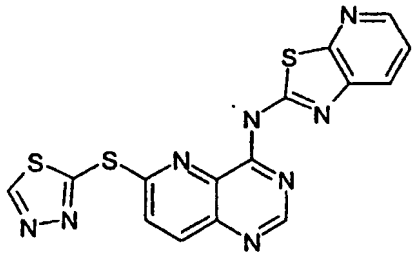
[6-(pyridin-2-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine

The compound of Example 51 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using 2-mercapto-pyridine, thiazolo [5,4-b] pyridine-2-yl-amine and 4,6-dichloro-pyrido [3,2-d] pyrimidine.

1H-NMR(CDCl3) δ 7.39-7.45 (2H, m), 7.67-7.70 (1H, m), 7.80 (1H, d, J = 8.8 Hz), 7.82-7.87 (1H, m), 8.06-8.08 (1H, m), 8.14 (1H, d, J = 8.8 Hz), 8.48-8.50 (1H, m), 8.67-8.69 (1H, m), 8.97 (1H, s).

ESI-MS (m/e): 390 (M+H)+.

Example 52



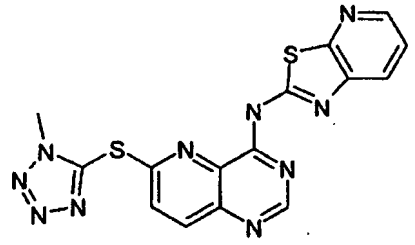
[6-(1,3,4-thiadiazol-2-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine

The compound of Example 52 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using 2-mercapto-[1,3,4] thiadiazole, thiazolo [5,4-b] pyridine-2-yl-amine and 4,6-dichloro-pyrido [3,2-d] pyrimidine.

1H-NMR (DMSO) δ 7.46 (1H, dd, J = 4.8, 8.4 Hz), 7.91 (1H, d, J = 8.8 Hz), 8.10 (1H, dd, J = 1.6, 8.4 Hz), 8.29 (1H, d, J = 8.8 Hz), 8.53 (1H, dd, J = 1.6, 4.8 Hz), 9.04 (1H, s), 9.52 (1H, s).

ESI-MS (m/e): 397 (M+H)+.

Example 53



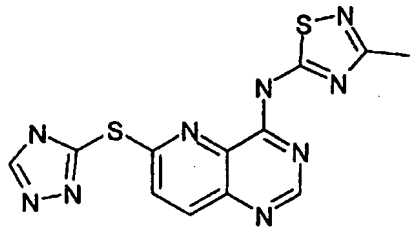
[6-(1-methyl-1H-tetrazol-5-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine

The compound of Example 53 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using 5-mercapto-1-methyl-1H-tetrazole, thiazolo [5,4-b] pyridine-2-yl-amine and 4,6-dichloro-pyrido [3,2-d] pyrimidine.

1H-NMR (DMSO) δ 4.15 (3H, s), 7.56 (1H, dd, J = 4.6, 8.2 Hz), 7.96 (1H, d, J = 8.8 Hz), 8.19-8.22 (1H, m), 8.37 (1H, d, J = 8.8 Hz), 8.52 (1H, dd, J = 1.6, 4.6 Hz), 9.03 (1H, s).

ESI-MS (m/e): 395 (M+H)+.

Example 54



[6-(4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-3-methyl-[1,2,4] thiadiazol-5-yl-amine

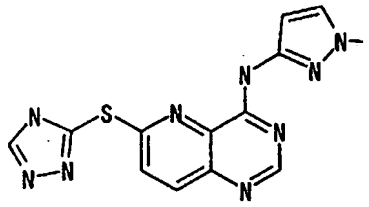
The compound of Example 54 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using 3-mercapto-4H-[1,2,4] triazole, 5-amino-3-methyl-[1,2,4] thiadiazole and 4,6-dichloro-pyrido [3,2-d] pyrimidine.

3-mercapto-4H-[1,2,4] triazole 54 mg (0.54 mmol) and (6-chloro-pyrido [3,2-d] pyrimidine-4-yl)-3-methyl-[1,2,4] thiadiazol-5-yl-amine 100 mg (0.36 mmol) were added to N,N-dimethylacetamide solution (3 ml) of potassium t-butoxide 80 mg (0.72 mmol) and thereafter, the mixture was stirred at 130°C for 16 hours. Water was added to the reaction liquor, and extraction was carried out with chloroform. The organic layer was dried and concentrated, thereafter the obtained residue was purified using reverse phase separation HPLC (0.1 % TFA-containing water : acetonitrile = 90 : 10 to 10 : 90), and the title compound 3 mg (yield: 2 %) was obtained as a yellow solid.

1H-NMR (DMSO) δ 2.53 (3H, s), 7.61 (1H, s), 8.25-8.27 (2H, m), 8.94 (1H, s).

ESI-MS (m/e): 344 (M+H)+.

Example 55



[6-(4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine

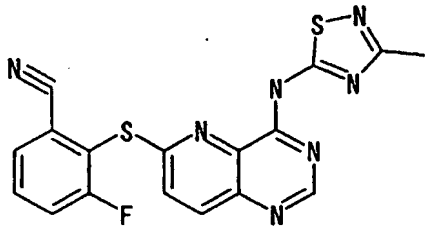
The compound of Example 55 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using 3-mercapto-[1,2,4] triazole, 3-amino-1-methyl-1H-pyrazole and 4,6-dichloro-pyrido [3,2-d] pyrimidine.

3-mercapto-4H-[1,2,4] triazole 128 mg (1.27 mmol) and (6-chloro-pyrido [3,2-d] pyrimidine-4-yl)-3-amino-1-methyl-1H-pyrazole 110 mg (0.42 mmol) were added to N,N-dimethylacetamide solution (5 ml) of potassium t-butoxide 120 mg (1.06 mmol) and thereafter, the mixture was stirred at 130°C for five hours. Water was added to the reaction liquor, and extraction was carried out with chloroform. The organic layer was dried and concentrated, thereafter the obtained residue was purified using reverse phase separation HPLC (0.1 % TFA-containing water : acetonitrile = 90 : 10 to 10 : 90), and the title compound 57 mg (yield: 33 %) was obtained as a yellow solid.

1H-NMR (DMSO) δ 3.84 (3H, s), 6.79 (1H, 3.6 Hz = d), 7.62 (1H, d, J = 8.8 Hz), 7.73 (1H, d, J = 3.6 Hz), 8.12 (1H, d, J = 8.8 Hz), 8.73 (1H, s), 8.84 (1H, s).

ESI-MS (m/e): 326 (M+H)+.

Example 56



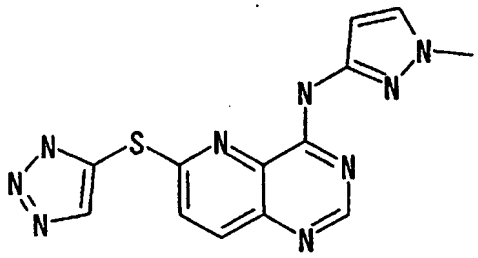
[6-(3-fluoro-benzonitrile-2-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-3-methyl-[1,2,4] thiadiazol-5-yl-amine

The compound of Example 56 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using 3-fluoro-2-mercapto-benzonitrile, 5-amino-3-methyl-[1,2,4] thiadiazole and 4,6-dichloro-pyrido [3,2-d] pyrimidine.

1H-NMR (CDCl3) δ : 2.59 (3H, s), 7.59-7.64 (1H, m), 7.68 (1H, d, J = 9.0 Hz), 7.75-7.79 (2H, m), 8.20 (1H, d, J = 9.0 Hz), 8.98 (1H, s).

ESI-MS (m/e): 396 (M+H)+.

Example 57



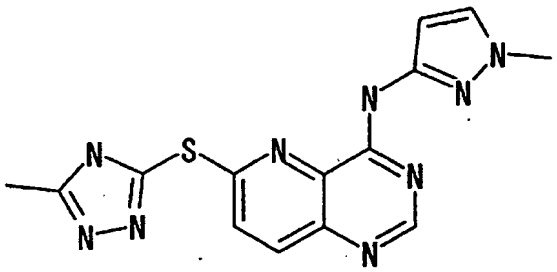
[6-(3H-[1,2,3] triazol-4-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-(1-methyl-1H-pyrazole-3-yl)-amine

The compound of Example 57 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using 4-mercapto-3H-[1,2,3] triazole, 3-amino-1-methyl-1H-pyrazole and 4,6-dichloro-pyrido [3,2-d] pyrimidine.

1H-NMR (CDCl3) δ : 3-90 (3H, s), 7.03 (1H, d, J = 2.3 Hz), 7.38 (1H, d, J = 2.3 Hz), 7.49 (1H, d, J = 9.0 Hz), 7.98-8.00 (2H, m), 8.69 (1H, s).

ESI-MS (m/e): 326 (M+H)+.

Example 58



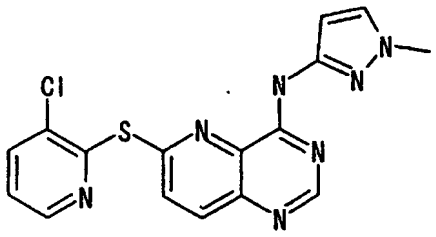
[6-(5-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine

The compound of Example 58 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using 3-mercapto-5-methyl-4H-[1,2,4] triazole, 3-amino-1-methyl-1H-pyrazole and 4,6-dichloro-pyrido [3,2-d] pyrimidine.

1H-NMR (CDCl3) δ : 2.57 (3H, s), 3.90 (3H, s), 7.04 (1H, d, J = 2.3 Hz), 7.38 (1H, d, J = 2.3 Hz), 7.62 (1H, d, J = 8.8 Hz), 8.00 (1H, d, J = 8.8 Hz), 8.70 (1H, s).

ESI-MS (m/e): 340 (M+H)+.

Example 59



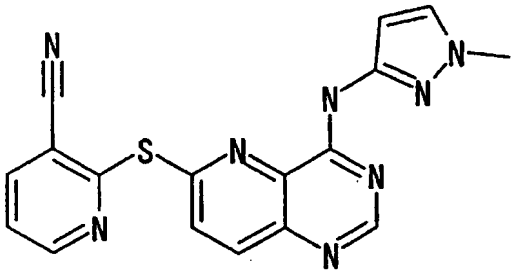
[6-(3-chloro-pyridin-2-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine

The compound of Example 59 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using 3-chloro-2-mercapto-pyridine, 3-amino-1-methyl-1H-pyrazole and 4,6-dichloro-pyrido [3,2-d] pyrimidine.

1H-NMR (CDCl3) δ : 3.86 (3H, s), 6.98 (1H, d, J = 2.3 Hz), 7.17-7.18 (1H, m), 7.34 (1H, d, J = 2-3 Hz), 7.74 (1H, dd, J = 8.2, 1.6 Hz), 7.81 (1H, d, J = 8.6 Hz), 8.06 (1H, d, J = 8.6 Hz), 8.35 (1H, dd, J = 4.5, 1.6 Hz), 8.75 (1H, s), 9.24 (1H, s).

ESI-MS (m/e): 370 (M+H)+.

Example 60

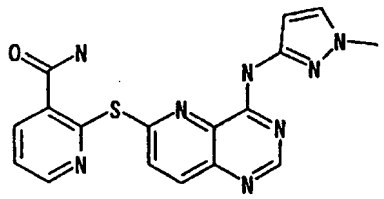


[6-(3-cyano-pyridin-2-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine

The compound of Example 60 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using 3-cyano-2-mercapto-pyridine, 3-amino-1-methyl-1H-pyrazole and 4,6-dichloro-pyrido [3,2-d] pyrimidine.

1H-NMR (DMSO-d6) δ : 3.82 (3H, s), 6.78 (1H, d, J = 2.2 Hz), 7.63-7.65 (1H, m), 7.72 (1H, d, J = 2.2 Hz), 8.03 (1H, d, J = 8.8 Hz), 8.21 (1H, d, J = 8.8 Hz), 8.48-8.50 (1H, m), 8.76 (1H, s), 8.79-8.79 (1H, m).
ESI-MS (m/e): 361 (M+H)+.

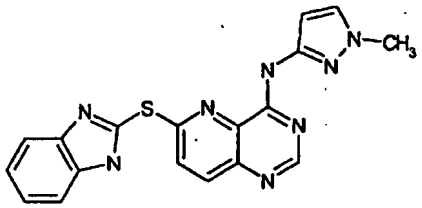
Example 61



[6-(3-amide-pyridin-2-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine

The compound of Example 61 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using 3-carbamoyl-2-mercapto-pyridine, 3-amino-1-methyl-1H-pyrazole and 4,6-dichloro-pyrido [3,2-d] pyrimidine.
1H-NMR(CD3OD) δ : 3.80 (3H, s), 6.86 (1H, d, J = 2.2 Hz), 7.27-7.30 (2H, m), 7.71 (1H, d, J = 8.8 Hz), 7.95 (1H, d, J = 8.8 Hz), 8.00-8.02 (1H, m), 8.46-8.48 (1H, m), 8.60 (1H, s).
ESI-MS (m/e): 379 (M+H)+.

Example 62

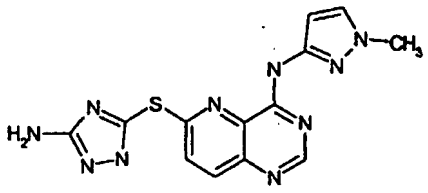


6-(1H-benzimidazol-2-yl sulphanyl)-N-(1-methyl-1H-pyrazol-3-yl) pyrido (3,2-d) pyrimidine-4-yl-amine

The compound of Example 62 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using 2-mercapto-1H-benzimidazole, 3-amino-1-methyl-1H-pyrazole and 4,6-dichloro-pyrido [3,2-d] pyrimidine.
1H-NMR (CDCl3) δ : 3.94 (3H, s), 6.99 (1H, d, J = 3.1 Hz), 7.45-7.51 (3H, m), 7.70-7.73 (2H, m), 7.99 (1H, d, J = 8.6 Hz), 8.34 (1H, d, J = 8.6 Hz), 8.75 (1H, s).

ESI-MS (m/e): 375 (M+H)+.

Example 63



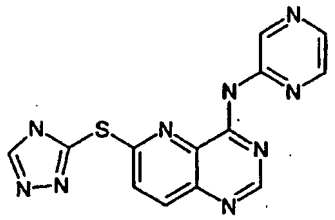
6-[(5-amino-4H-1,2,4-triazol-3-yl) sulphanyl]-N-(1-methyl-1H-pyrazol-3-yl) pyrido (3,2-d) pyrimidine-4-yl-amine

The compound of Example 63 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using 5-amino-3-mercapto-4H-[1,2,4] triazole, 3-amino-1-methyl-1H-pyrazole and 4,6-dichloro-pyrido [3,2-d] pyrimidine.

1H-NMR(CD3OD) δ : 3.89 (3H, s), 6.93 (1H, d, J = 2.0 Hz), 7.59 (1H, d, J = 2.0 Hz), 7.68 (1H, d, J = 9.0 Hz), 8.03 (1H, d, J = 9.0 Hz), 8.63 (1H, s).

ESI-MS (m/e): 341 (M+H).

Example 64



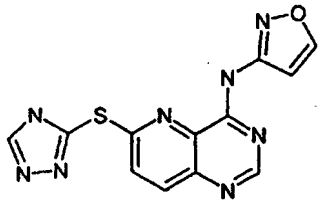
N-pyrazine-2-yl-6-(4H-1,2,4-triazol-3-yl sulphanyl) pyrido (3,2-d) pyrimidine-4-yl-amine

The compound of Example 64 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using 3-mercapto-4H-[1,2,4] triazole, 2-amino-pyrazine and 4,6-dichloro-pyrido [3,2-d] pyrimidine.

1H-NMR(CD3OD) δ : 7.77 (1H, d, J = 9.0 Hz), 8.15 (1H, d, J = 9.0 Hz), 8.39 (1H, d, J = 2.3 Hz), 8.45-8.48 (1H, m), 8.75 (1H, s), 8.84 (1H, s), 9.99 (1H, s).

ESI-MS (m/e): 324 (M+H).

Example 65



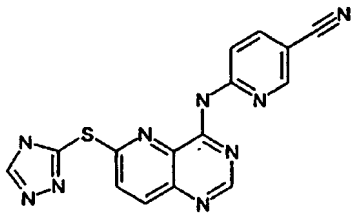
N-isoxazol-3-yl-6-(4H-1,2,4-triazol-3-yl sulphanyl) pyrido (3,2-d) pyrimidine-4-yl-amine

The compound of Example 65 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using 3-mercapto-4H-[1,2,4] triazole, 3-aminooxazole and 4,6-dichloro-pyrido [3,2-d] pyrimidine.

1H-NMR(CD3OD) δ : 7.37 (1H, d, J = 1.6 Hz), 7.69 (1H, d, J = 8.6 Hz), 8.10 (1H, d, J = 9.0 Hz), 8.65 (1H, d, J = 1-6 Hz), 8.72 (1H, s), 8.75 (1H, s).

ESI-MS (m/e): 313 (M+H).

Example 66



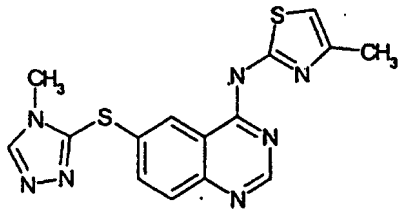
6-{[6-(4H-1,2,4-triazol-3-yl sulphanyl) pyrido [3,2-d] pyrimidin-4-yl] amino} nicotino nitrile

The compound of Example 66 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using 3-mercapto-4H-[1,2,4] triazole, 2-amino-5-cyano-pyridine and 4,6-dichloro-pyrido [3,2-d] pyrimidine.

1H-NMR (DMSO-d6) δ : 7.72-7.75 (1H, m), 8.24 (1H, d, J = 9.0 Hz), 8.39-8.41 (1H, m), 8.80 (1H, d, J = 9.0 Hz), 8.85-8.93 (2H, m), 9.62 (1H, s).

ESI-MS (m/e): 348 (M+H).

Example 67



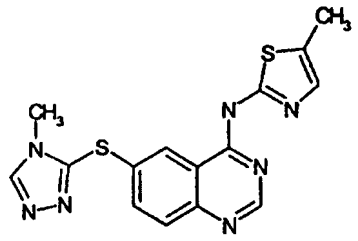
(4-methyl-1,3-thiazol-2-yl)-6-(4-methyl-1,2,4-triazol-3-yl sulphanyl)-quinazoline-4-yl-amine

The compound of Example 67 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure using 3-mercapto-4-methyl-[1,2,4] triazole, 2-amino-4-methyl-1,3-thiazole and 4-chloro-6-iodo quinazoline.

1H-NMR(CDCl3). δ : 2.40 (3H, s), 3.66 (3H, s), 6.55 (1H, s), 7.64 (2H, brs), 8.25 (1H, brs), 8.31 (1H, s), 8.46 (1H, s).

ESI-MS (m/e): 354 (M+H)+.

Example 68



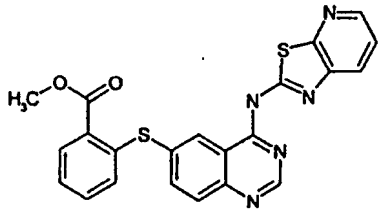
(5-methyl-1,3-thiazol-2-yl)-6-(4-methyl-1,2,4-triazol-3-yl sulphanyl)-quinazoline-4-yl-amine

The compound of Example 68 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure using 3-mercapto-4-methyl-[1,2,4] triazole, 2-amino-5-methyl-1,3-thiazole and 4-chloro-6-iodo quinazoline.

1H-NMR(CDCl3) δ : 2.43 (3H, s), 3.65 (3H, s), 7.13 (1H, s), 7.62 (2H, brs), 8.25 (1H, brs), 8.31 (1H, s), 8.46 (1H, s).

ESI-MS (m/e): 354 (M+H)+.

Example 69



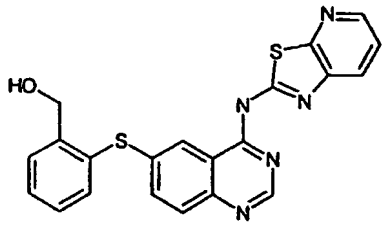
6-(methyl benzoate-2-yl sulphanyl)-thiazolo [5,4-b] pyridin-2-yl quinazoline-4-yl-amine

The compound of Example 69 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure using 2-mercapto-methyl benzoate ester, thiazolo [5,4-b] pyridine-2-yl-amine and 4-chloro-6-iodo quinazoline.

1H-NMR(CD3OD) δ : 3.99 (3H, s), 6.96 (1H, d, J = 8.4 Hz), 7.23-7.27 (1H, m), 7.32-7.36 (1H, m), 7.44-7.48 (1H, m), 7.91 (1H, brs), 8.02-8.08 (4H, m), 8.45-8.46 (1H, s), 8.78 (1H, s).

ESI-MS (m/e): 446 (M+H)+.

Example 70



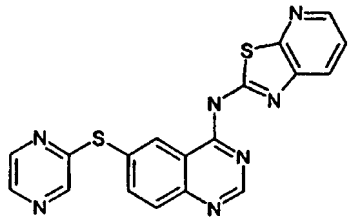
6-(2-hydroxymethyl phenyl sulphanyl)-thiazolo [5,4-b] pyridin-2-yl quinazoline-4-yl-amine

The compound of Example 70 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure using 2-hydroxymethyl-thiophenol, thiazolo [5,4-b] pyridine-2-yl-amine and 4-chloro-6-iodo quinazoline.

1H-NMR(CD3OD) δ : 4.83 (2H, s), 7.32 (1H, t, J = 7.2 Hz), 7.4.6-7.48 (3H, m), 7.57 (1H, d, J = 8.4 Hz), 7.67 (1H, d, J = 7.2 Hz), 7.72 (1H, d, J = 8.4 Hz), 8.04 (1H, brs), 8.37 (1H, brs), 8.43 (1H, brs), 8.67 (1H, brs).

ESI-MS (m/e): 418 (M+H)+.

Example 71



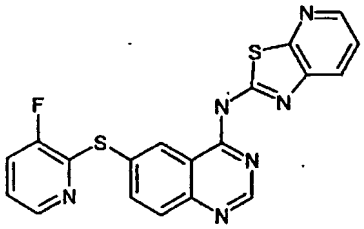
6-(pyrazin-2-yl sulphanyl)-thiazolo [5,4-b] pyridin-2-yl quinazoline-4-yl-amine

The compound of Example 71 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure using 2-mercapto-pyrazine, thiazolo [5,4-b] pyridine-2-yl-amine and 4-chloro-6-iodo quinazoline.

1H-NMR (DMSO) δ : 7.51-7.54 (1H, m), 7.97 (1H, brs), 8.07-8.34 (3H, m), 8.48-8.52 (3H, m), 8.60 (1H, d, J = 1.6 Hz), 8.99 (1H, brs).

ESI-MS (m/e): 390 (M+H)+.

Example 72



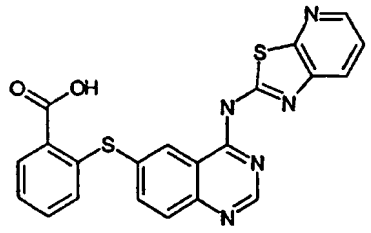
6-(3-fluoropyridin-2-yl sulphanyl)-thiazolo [5,4-b] pyridin-2-yl quinazoline-4-yl-amine

The compound of Example 72 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure using 3-fluoro-2-mercapto-pyridine, thiazolo [5,4-b] pyridine-2-yl-amine and 4,6-dichloro-pyrido [3,2-d] pyrimidine.

1H-NMR(CD3OD) δ : 7.21-7.25 (1H, m), 7.43-7.48 (3H, m), 7.86-7.96 (2H, m), 8.06 (1H, d, J = 7.2 Hz), 8.21-8.24 (1H, m), 8.43 (1H, d, J = 4.8 Hz), 8.73 (1H, d, J = 1.6 Hz).

ESI-MS (m/e): 407 (M+H)+.

Example 73



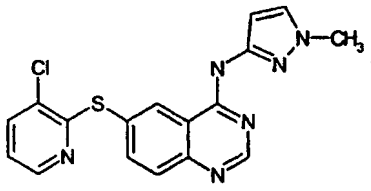
6-(benzoate-2-yl sulphanyl)-thiazolo [5,4-b] pyridin-2-yl quinazoline-4-yl-amine

The compound of Example 73 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure using 2-mercapto-benzoic acid, thiazolo [5,4-b] pyridine-2-yl-amine and 4-chloro-6-iodo quinazoline.

1H-NMR (DMSO) δ : 6.89 (1H, d, J = 8.0 Hz), 7.28 (1H, t, J = 8.0 Hz), 7.39 (1H, t, J = 8.0 Hz), 7.55 (1H, dd, J = 8.0, 4.8 Hz), 7.95-8.08 (4H, m), 8.52 (1H, dd, J = 4.8, 1.6 Hz), 8.90 (1H, brs), 9.13 (1H, s).

ESI-MS (m/e): 432 (M+H) +.

Example 74



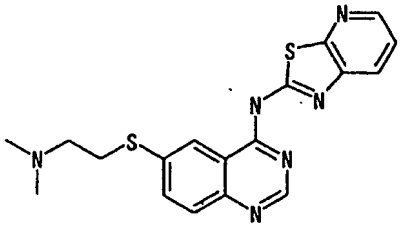
6-(3-chloropyridin-2-yl sulphanyl)-(1-methylpyrazol-3-yl) quinazoline-4-yl-amine

The compound of Example 74 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure using 3-chloro-2-mercapto-pyridine, 3-amino-1-methylpyrazole and 4-chloro-6-iodo quinazoline.

1H-NMR(CD3OD) δ : 3.88 (1H, s), 6.88 (1H, d, J = 2.0 Hz), 7.07-7.10 (1H, m), 7.43 (1H, d, J = 2.0 Hz), 7.69 (1H, dd, J = 8.0, 1.6 Hz), 7.85 (1H, d, J = 8.8 Hz), 7.90 (1H, dd, J = 8.8, 2.0 Hz), 8.20 (1H, dd, J = 4.8, 1.6 Hz), 8.49 (1H, d, J = 1.6 Hz), 8.69 (1H, s).

ESI-MS (m/e): 369 (M+H)+.

Example 75



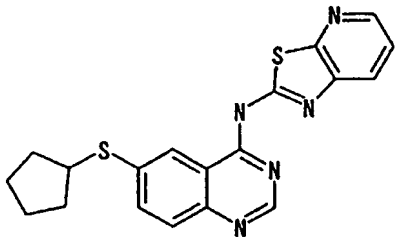
[6-(2-dimethylamino-ethyl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine

The compound of Example 75 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure using 2-dimethylamino ethanethiol, thiazolo [5,4-b] pyridine-2-yl-amine and 4-chloro-6-iodo quinazoline.

1H-NMR (DMSO) δ 2.86 (6H, s), 3.36-3.38 (2H, m), 3.53-3.56 (2H, m), 7.54 (1H, dd, J = 4.0, 8.0 Hz), 7.89 (1H, d, J = 8.8 Hz), 7.98 (1H, d, J = 8.8 Hz), 8.13 (1H, d, J = 8.0 Hz), 8.51 (1H, d, J = 4.0 Hz), 8.69 (1H, s), 8.92 (1H, s), 9.58 (1H, s).

ESI-MS (m/e): 383 (M+H)+.

Example 76



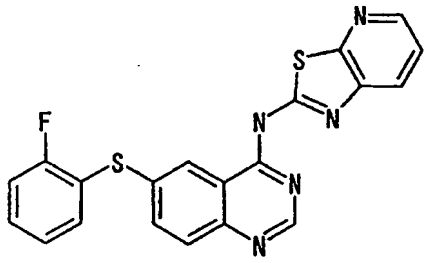
[6-(cyclopentyl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine

The compound of Example 76 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure using cyclopentane thiol, thiazolo [5,4-b] pyridine-2-yl-amine and 4-chloro-6-iodo quinazoline.

1H-NMR (DMSO) δ 1.57-1.78 (6H, m), 2.19-2.23 (2H, m), 4.04-4.07 (1H, m), 7.53-7.57 (1H, m), 7.83-7.88 (2H, m), 8.11-8.14 (1H, m), 8.49-8.51 (1H, m), 8.60 (1H, s), 8.94 (1H, s).

ESI-MS (m/e): 380 (M+H)+.

Example 77



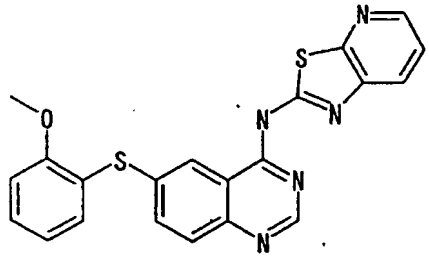
[6-(2-fluorophenyl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine

The compound of Example 77 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure using 2-fluoro-thiophenol, thiazolo [5,4-b] pyridine-2-yl-amine and 4-chloro-6-iodo quinazoline.

1H-NMR (DMSO) δ 7.26-7.30 (1H, m), 7.36-7.41 (1H, m), 7.46-7.52 (3H, m), 7.56-7.84 (2H, m), 8.04-8.09 (1H, m), 8.45-8.50 (1H, m), 8.72-8.88 (1H, m), 8.93 (1H, s).

ESI-MS (m/e): 406 (M+H)+.

Example 78



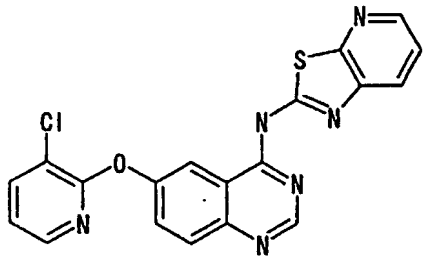
[6-(2-methoxyphenyl sulphanyl)-quinazoline-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine

The compound of Example 78 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure using 2-methoxy-thiophenol, thiazolo [5,4-b] pyridine-2-yl-amine and 4-chloro-6-iodo quinazoline.

1H-NMR (DMSO) δ 3.83 (3H, s), 6.99-7.03 (1H, m), 7.19 (1H, d, J = 8.0 Hz), 7.26 (1H, d, J = 8.0 Hz), 7.40-7.44 (1H, m), 7.52-7.58 (1H, m), 7.68-7.74 (1H, m), 7.82-7.88 (1H, m), 8.06-8.12 (1H, m), 8.48-8.54 (1H, m), 8.72-8.78 (1H, m), 8.92-8.99 (1H, m).

ESI-MS (m/e): 418 (M+H)+.

Example 79



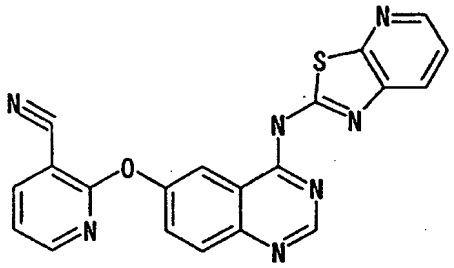
[6-(3-chloropyridine-2-yloxy)-quinazoline-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine

The compound of Example 79 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2,3-dichloropyridine, thiazolo [5,4-b] pyridine-2-yl-amine and 4-chloro-6-hydroxy-quinazoline.

1H-NMR (DMSO) δ 7.30 (1H, dd, J = 4.8, 7.6 Hz), 7.54 (1H, dd, J = 4.8, 7.6 Hz), 7.91 (1H, dd, J = 2.4, 8.8 Hz), 8.01 (1H, d, J = 8.8 Hz), 8.08-8.10 (1H, m), 8.15-8.20 (2H, m), 8.51 (1H, dd, J = 1.2, 4.8 Hz), 8.55 (1H, s), 9.00 (1H, s).

ESI-MS (m/e): 407 (M+H)+.

Example 80



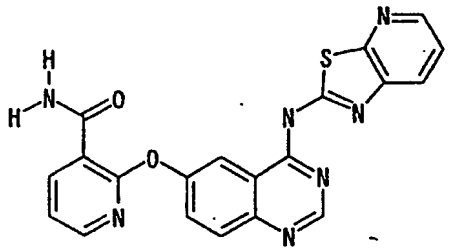
[6-(3-cyanopyridine-2-yloxy)-quinazoline-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine

The compound of Example 80 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 3-cyano-2-chloropyridine, thiazolo [5,4-b] pyridine-2-yl-amine and 4-chloro-6-hydroxy-quinazoline.

1H-NMR (DMSO) δ 7.41 (1H, dd, J = 4.8, 7.6 Hz), 7.52 (1H, dd, J = 4.8, 8.4 Hz), 7.94-8.02 (2H, m), 8.07-8.09 (1H, m), 8.44 (1H, dd, J = 1.6, 4.8 Hz), 8.48 (1H, dd, J = 1.6, 4.8 Hz), 8.52 (1H, dd, J = 1.6, 7.6 Hz), 8.64 (1H, s), 8.98 (1H, s).

ESI-MS (m/e): 398 (M+H)+.

Example 81



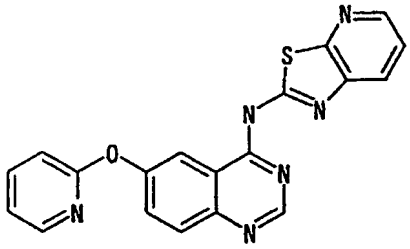
[6-(3-carboxamide pyridine-2-yloxy)-quinazoline-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine

The compound of Example 81 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 3-carbamoyl-2-chloropyridine, thiazolo [5,4-b] pyridine-2-yl-amine and 4-chloro-6-hydroxy-quinazoline.

1H-NMR (DMSO) δ 7.30-7.33 (1H, m), 7.44-7.49 (1H, m), 7.80-7.87 (2H, m), 7.90-7.97 (2H, m), 7.99-8.041(1H, m), 8.23-8.27 (2H, m), 8.40-8.44 (1H, m), 8.50-8.56 (1H, m), 8.84-8.90 (1H, m).

ESI-MS (m/e): 416 (M+H)+.

Example 82



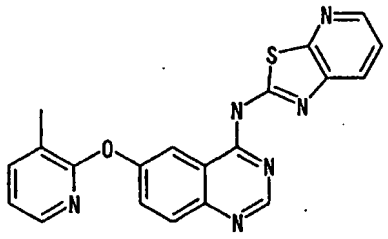
[6-(pyridine-2-yloxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine

Compound of Example 82 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2-fluoropyridine, thiazolo [5,4-b] pyridine-2-yl-amine and 4-chloro-6-hydroxy-quinazoline.

1H-NMR (DMSO) δ 7.24-7.27 (2H, m), 7.54 (1H, dd, = 4.8, 8.0 Hz), 7.84 (1H, dd, J = 2.4, 8.8 Hz), 7.96-8.00 (2H, m), 8.07-8.09 (1H, m), 8.22-8.24 (1H, m), 8.50-8.51 (2H, m), 8.99 (1H, s).

ESI-MS (m/e): 373 (M+H)+.

Example 83



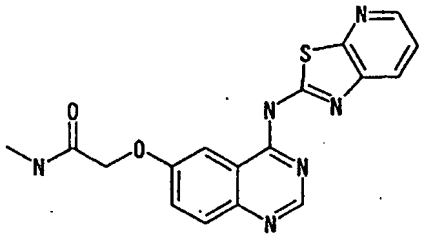
[6-(3-methylpyridine-2-yloxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine

The compound of Example 83 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2-chloro-3-methylpyridine, thiazolo [5,4-b] pyridine-2-yl-amine and 4-chloro-6-hydroxy-quinazoline.

1H-NMR (DMSO) δ 2.45 (3H, s), 7.19-7.22 (1H, m), 7.59-7.62 (1H, m), 7.83-7.85 (1H, m), 7.93-7.95 (2H, m), 8.03-8.06 (2H, m), 8.34-8.35 (1H, m), 8.58-8.59 (1H, m), 9.10 (1H, s).

ESI-MS (m/e): 387 (M+H)+.

Example 84



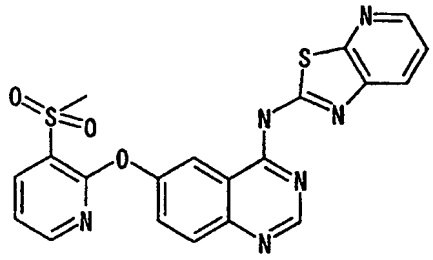
[6-(methylcarbamoyl-methyl oxy)-quinazoline-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine

The compound of Example 84 was produced by the same process as in Example 22, a process based on this or a combination of these and a normal procedure using 2-hydroxy-N-methyl-acetamide, thiazolo [5,4-b] pyridine-2-yl-amine and 4-chloro-6-hydroxy-quinazoline.

1H-NMR (DMSO) δ 2.73 (3H, d, J = 4.4 Hz), 4.72 (2H, s), 7.55 (1H, dd, J = 4.8, 8.0 Hz), 7.71-7.74 (1H, m), 7.93 (1H, d, J = 8.8 Hz), 8.12-8.13 (1H, m), 8.20-8.24 (1H, m), 8.50-8.51 (1H, m), 8.92 (1H, s).

ESI-MS (m/e): 367 (M+H)+.

Example 85



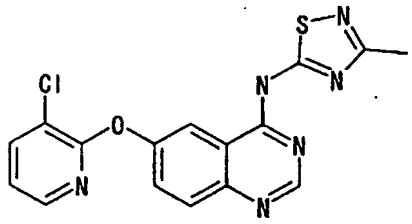
[6-(3-methylsulfonyl pyridine-2-yloxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine

The compound of Example 85 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2-chloro-3-methylsulfonyl pyridine.

1H-NMR (DMSO) δ 3.55 (3H, s), 7.49-7.55 (2H, m), 7.96-8.10 (3H, m), 8.44 (1H, dd, J = 2.0, 7.6 Hz), 8.48-8.51 (2H, m), 8.64 (1H, s), 9.01 (1H, s).

ESI-MS (m/e): 451 (M+H)+.

Example 86



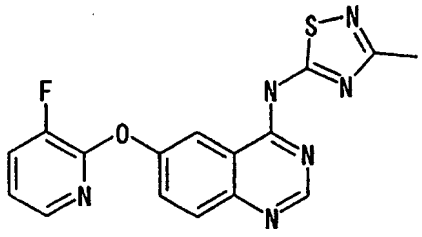
[6-(3-chloropyridine-2-yloxy)-quinazolin-4-yl]-3-methyl-[1,2,4] thiadiazol-5-yl-amine

The compound of Example 86 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2,3-dichloropyridine, 5-amino-3-methyl-[1,2,4] thiadiazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CDCl3) δ 2.58 (3H, s), 7.09-7.12 (1H, m), 7.76-7.78 (1H, m), 7.86-7.89 (1H, m), 8.04-8.08 (2H, m), 8.19 (1H, s), 8.98 (1H, s).

ESI-MS (m/e): 371 (M+H)+.

Example 87



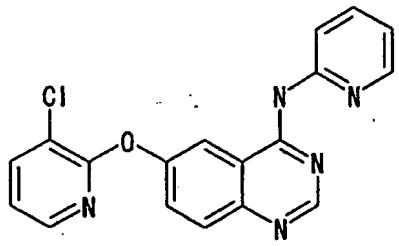
[6-(3-fluoropyridine-2-yloxy)-quinazoline-4-yl]-3-methyl-[1,2,4] thiadiazol-5-yl-amine

The compound of Example 87 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2-chloro-3-fluoropyridine, 5-amino-3-methyl-[1,2,4] thiadiazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CDCl3) δ 2.56 (3H, s), 7.12-7.16 (1H, m), 7.57-7.62 (1H, m), 7.78 (1H, dd, J = 2.4, 8.8 Hz), 7.95-7.97 (1H, m), 8.09 (1H, d, J = 8.8 Hz), 8.17 (1H, d, J = 2.4 Hz), 8.99 (1H, s).

ESI-MS (m/e): 355 (M+H)+.

Example 88



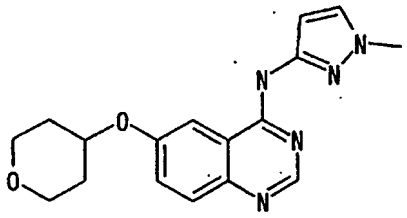
[6-(3-chloropyridine-2-yloxy)-quinazolin-4-yl] - pyridine-2-yl-amine

The compound of the Example was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2,3-dichloropyridine, 2-aminopyridine and 4-chloro-6-hydroxy-quinazoline.

1H-NMR (CDCl3) δ : 7.07 (1H, dd, J = 7.6, 4.9 Hz), 7.25-7.25 (1H, m), 7.33-7.35 (1H, m), 7.49-7.52 (2H, m), 7.77 (1H, dd, J = 9.2, 2.5 Hz), 7.85 (1H, dd, J = 7.6, 1.8 Hz), 8.07-8.10 (2H, m), 8.16 (1H, d, J = 2.5 Hz), 8.78 (1H, s).

ESI-MS (m/e): 350 (M+H)+.

Example 89



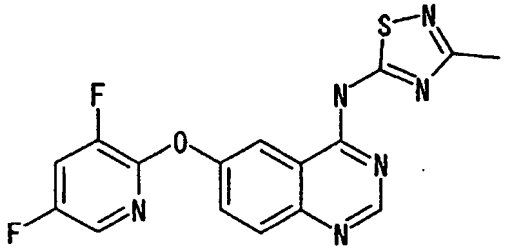
[6-(tetrahydro-2H-pyran-4-yloxy)-quinazoline-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine

The compound of Example 89 was produced by the same process as in Example 22, a process based on this or a combination of these and a normal procedure using 4-hydroxy-tetrahydro-2H-furan, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR (CDCl3) δ : 1.79-1.82 (2H, m), 2.1.5-2.18 (2H, m), 3.73-3.75 (2H, m), 3.91 (3H, s), 3.97-4.03 (2H, m), 5.00-5.02 (1H, m), 6.91-6.93 (1H, m), 7.39-7.40 (1H, m), 7.52 (1H, dd, J = 9.2, 2.5 Hz), 8.02 (1H, d, J = 9.2 Hz), 8.25 (1H, s), 8.60 (1H, s).

ESI-MS (m/e): 326 (M+H)+.

Example 90



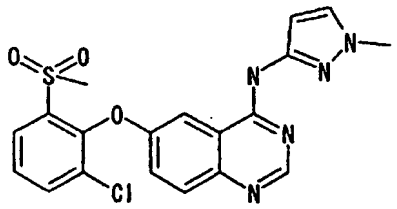
[6-(3,5-difluoro pyridine-2-yloxy)-quinazolin-4-yl]-3-methyl-[1,2,4] thiadiazol-5-yl-amine

The compound of Example 90 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2,3,5-trifluoropyridine, 5-amino-3-methyl-[1,2,4] thiadiazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR (CDCl3) δ : 2.59 (3H, s), 7.47-7.49 (1H, m), 7.77 (1H, dd, J = 9.0, 2.5 Hz), 7.90 (1H, d, J = 2.5 Hz), 8.09 (1H, d, J = 9.0 Hz), 8.16 (1H, d, J = 2.5 Hz), 9.00 (1H, s).

ESI-MS (m/e): 373 (M+H)+.

Example 91



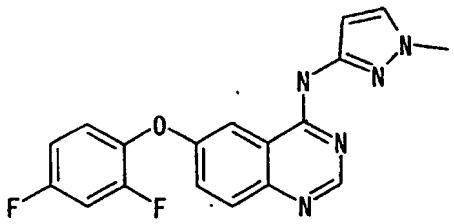
6-(2-chloro-6-(methylsulfonyl) phenoxy)-quinazolin-4-yl]- (1-methyl-1H-pyrazol-3-yl) -amine

The compound of Example 91 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 1,2-dichloro-3-methylsulfonyl benzene, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR (CDCl3) δ : 3.31 (3H, s), 3.84 (3H, s), 6.78 (1H, d, J = 2.2 Hz), 7.31 (1H, d, J = 2.2 Hz), 7.45-7.55 (2H, m), 7.79 (2H, dd, J = 8.0, 1.7 Hz), 7.95 (1H, d, J = 9.0 Hz), 8.08 (1H, dd, J = 8.0, 1.7 Hz), 8.63 (1H, s).

ESI-MS (m/e): 430 (M+H)+.

Example 92



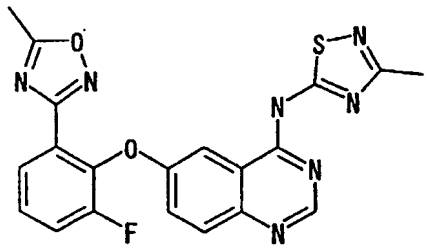
[6-(2,4-difluoro phenoxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine

The compound of Example 92 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 1,2,4-trifluorobenzene, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR (CDCl3) δ : 3.86 (3H, s), 6.86-7.00 (3H, m), 7.19-7.34 (2H,,m), 7.57-7.7.95 (3H, m), 8.77 (1H, s).

ESI-MS (m/e): 354 (M+H)+.

Example 93



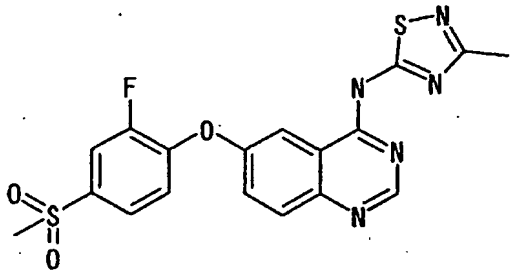
[6-(2-fluoro-6-(5-methyl-[1,2,4] oxadiazol-3-yl) phenoxy)-quinazolin-4-yl]-3-methyl-[1,2,4] thiadiazol-5-yl-amine

The compound of Example 93 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 3-(2,3-difluorophenyl)-5-methyl-1,2,4-oxadiazole, 5-amino-3-methyl-[1,2,4] thiadiazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR (DMSO-d6) δ : 1.63 (3H, s), 1.69 (3H, s), 6.68-6.70 (2H, m), 6.91 (1H, dd, J = 9.0, 2.7 Hz), 6.98-7.00 (1H, m), 7.07-7.09 (1H, m), 7.14-7.15 (1H, m), 7.99 (1H, s).

ESI-MS (m/e): 436 (M+H)+.

Example 94



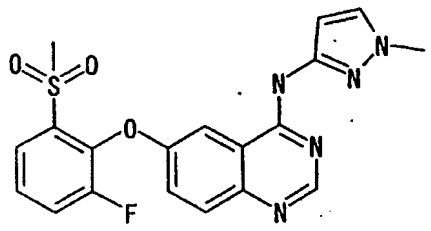
[6-(2-fluoro-4-(methylsulfonyl phenoxy)-quinazoline-4-yl]-3-methyl-[1,2,4] thiadiazol-5-yl-amine

The compound of Example 94 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 1,2-difluoro-4-methanesulphonyl benzene, 5-amino-3-methyl-[1,2,4] thiadiazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR (CDCl3) δ : 2.57 (3H, s), 3.16 (3H, s), 7.33-7.35 (1H, m), 7.72 (1H, dd, J = 9.0, 2.7 Hz), 7.81-7.83 (1H, m), 7.88-7.91 (2H, m), 8.10 (1H, d, J = 9.0 Hz), 9.00 (1H, s).

ESI-MS (m/e): 432 (M+H)+.

Example 95



[6-(2-fluoro-6-(methylsulfonyl) phenoxy)-quinazoline-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine

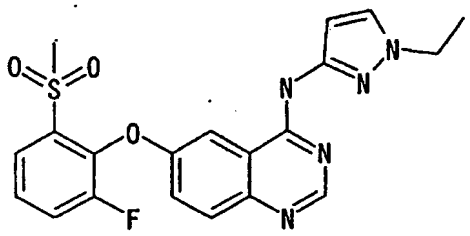
1,2-difluoro-3-iodobenzene 1.70 g (7.08 mmol), sodium methanesulfonate 2.17 g (21.2 mmol) and copper iodide 4.03 g (21.2 mmol) were heated with stirring in N,N-dimethylacetamide (50 ml) at 111°C for 20 hours. The reaction liquor was separated by filtration, chloroform was added to the filtrate, and washing was carried out with saturated aqueous sodium bicarbonate solution. The organic layer was dried and concentrated, and thereafter the obtained residue was purified using silica gel column chromatography (hexane : ethyl acetate = 2 : 1) and 1,2-difluoro-3-methanesulphonyl benzene 987 mg (yield: 72 %) was obtained as colourless transparent solution.

4-[(1-methyl-1H-pyrazol-3-yl) amino] quinazolin-6-ol 250 mg (1.033 mmol) and the obtained sulfone 424 mg (2.219 mmol)) were added to N,N-dimethylacetamide solution (24 ml) of potassium t-butoxide 320 mg (2.857 mmol), and thereafter the mixture was stirred at 77°C for 12 hours. Water was added to the reaction liquor, and extraction was carried out with chloroform. The organic layer was dried and concentrated, thereafter the obtained residue was purified using reverse phase separation HPLC (0.1 % TFA-containing water : acetonitrile = 90 : 10 to 10 : 90), and the title compound 120 mg (yield: 28 %) was obtained as a yellow solid.

1H-NMR (CDCl3) δ : 3.32 (3H, s), 3.85 (3H, s), 6.87 (1H, d, J = 2.3 Hz), 7.36 (1H, d, J = 2.3 Hz), 7.51-7.54 (2H, m), 7.71 (1H, dd, J = 9.0, 2.7 Hz), 7.82 (1H, d, J = 2.7 Hz), 7.93-7.95 (1H, m), 8.12 (1H, d, J = 9.0 Hz), 8.76 (1H, s).

ESI-MS (m/e): 414 (M+H)+.

Example 96



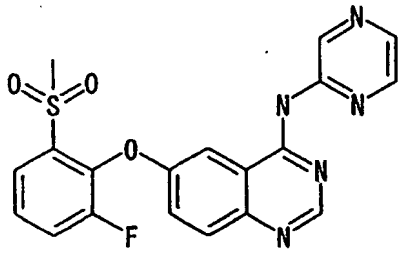
[6-(2-fluoro-6-(methylsulfonyl) phenoxy)-quinazoline-4-yl]-(1-ethyl-1H-pyrazol-3-yl)-amine

The compound of Example 96 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 1,2-difluoro-3-methanesulphonyl benzene, 3-amino-1-ethyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR (CDCl3) δ : 1.48 (3H, t, J = 7.4 Hz), 3.30 (3H, s), 4.12 (2H, q, J = 7.4 Hz), 6.82 (1H, d, J = 2.3 Hz), 7.37 (1H, d, J = 2.3 Hz), 7.49-7.57 (3H, m), 7.85-7.95 (3H, m), 8.58 (1H, s).

ESI-MS (m/e): 428 (M+H)+.

Example 97



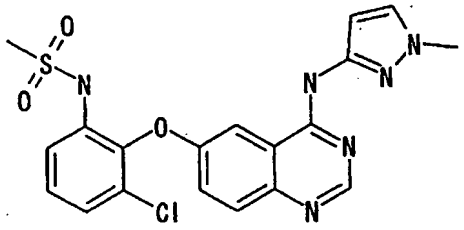
[6-(2-fluoro-6-(methylsulfonyl) phenoxy)-quinazolin-4-yl]-pyrazine-2-yl-amine

The compound of Example 97 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 1,2-difluoro-3-methanesulphonyl benzene, 2-aminopyrazine and 4-chloro-6-hydroxy-quinazoline.

1H-NMR (CDCl3) δ : 3.31 (3H, s), 7.48-7.53 (3H, m), 7.85-7.96 (3H, m), 8.31-8.34 (2H, m), 8.57 (1H, s), 9.31 (1H, s).

ESI-MS (m/e): 412 (M+H)+.

Example 98



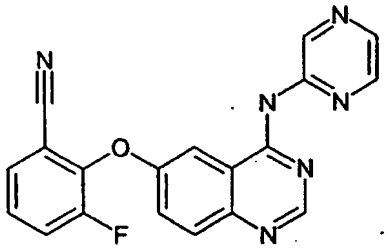
[6-(2-chloro-6-(methanesulphonyl amino) phenoxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine

The compound of Example 98 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using N-(3-chloro-2-fluorophenyl) methane sulfon amide, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR (DMSO-d6) δ : 2.95 (3H, s), 3.82 (3H, s), 6.74 (1H, s), 7.40-7.42 (1H, m), 7.47-7.49 (1H, m), 7.60 (1H, d, J = 8.3 Hz), 7.70-7.72 (2H, m), 7.87 (1H, d, J = 8.3 Hz), 7.96 (1H, s), 8.79 (1H, s), 9.71 (1H, s).

ESI-MS (m/e): 445 (M+H)+.

Example 99



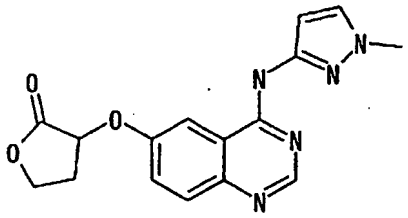
3-fluoro-2-({4-[[pyrazin-2-yl] amino] quinazolin-6-yl} oxy) benzonitrile

2-aminopyrazine 2.20 g (23.7 mmol), 2,2-bis diphenylphosphino-1,1-binaphthyl 0.49 g (0.8 mmol), cesium carbonate 10.2 g (31.5 mmol) and tris dibenzylideneacetone palladium 0.82 g (0.8 mmol) were added to toluene solution (180 ml) of 4-chloro-6-acetate-quinazoline 3.50 g (15.8 mmol), and thereafter the mixture was stirred at 111°C for 20 hours. The reaction liquor was separated by filtration, water was added to the filtrate, and extraction was carried out with chloroform. After drying and concentration of the organic layer, ammonia water 10 ml was added to the solution obtained by adding tetrahydrofuran 100 ml and methanol 100 ml to the obtained residue, and the mixture was stirred for 30 minutes. The reaction solution was concentrated, thereafter the obtained residue was stirred with

ethyl acetate solution, and thereafter the reaction solution was separated by filtration, the residue was dried, and 6-hydroxy-(pyrazine-2-yl) quinazoline-4-yl-amine 1.63 g (yield: 43 %) was obtained as a yellow solid.

Into N,N-dimethylacetamide solution (3 ml) of potassium tert-butoxide 89 mg (0.75 mmol) were added the obtained hydroxy body 60 mg (0.25 mmol) and 1,2-difluoro-benzonitrile 105 mg (0.75 mmol), and thereafter the mixture was stirred at room temperature for 45 minutes. Water was added to the reaction liquor, and extraction was carried out with chloroform. The organic layer was dried and concentrated, thereafter the obtained residue was purified using thin layer silica gel chromatography (chloroform : methanol = 9 : 1) and the title compound 36 mg (yield: 40 %) was obtained as a yellow solid.
1H-NMR (DMSO-d6) δ : 7.57-7.59 (1H, m), 7.87-7.92 (4H, m), 8.09-8.12 (1H, m), 8.34-8.37 (1H, m), 8.43-8.4.3 (1H, m), 8.70-8.72 (1H, m), 9.55 (1H, s), 10.64 (1H, s).
ESI-MS (m/e): 359 (M+H)+.

Example 100



[6-(butyl lactone-2-yloxy)-quinazoline-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine

4-chloro-6-hydroxy-quinazoline 77 mg (0.43 mmol), 2-hydroxy-butyl lactone 131 mg (1.28 mmol) and triphenylphosphine 336 mg (1.28 mmol) were dissolved in THF 7 ml, and diethylazo dicarboxylate 558 mg (1.28 mmol) was added at room temperature. The reaction liquor was stirred at room temperature furthermore for ten hours, and thereafter, water was added, and extraction was carried out with chloroform. The organic layer was dried and concentrated, and thereafter the obtained residue was purified using silica gel column chromatography (hexane : ethyl acetate = 1 : 1), and 4-chloro-6-(butyl lactone-2-yloxy)-quinazoline was obtained.

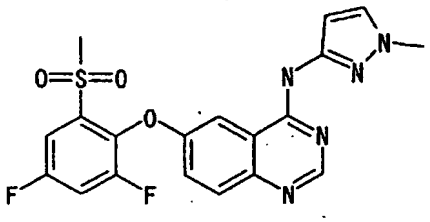
The obtained chloro body and 1-methyl-1H-pyrazole-3-amine 60 mg (0.147 mmol) were heated with stirring in phenol (0.2 ml) at 140°C for 30 minutes. Chloroform was added to the reaction liquor, and washed with saturated aqueous sodium bicarbonate solution. The organic layer was dried and concentrated, and thereafter the obtained residue was purified

using reverse phase separation HPLC (0.1 % TFA-containing water : acetonitrile = 90 : 10 to 10 : 90), and the title compound 1 mg (yield: 1 %) was obtained as a yellow solid.

1H-NMR (CDCl3) δ : 2.39-2.44 (1H, m), 2.95-2.96 (1H, m), 3.89 (3H, s), 4.39-4.46 (1H, m), 4.51-4.53 (1H, m), 5.35-5.38 (1H, m), 6.73-6.75 (1H, m), 7.32-7.33 (1H, m), 7.52-7.53 (1H, m), 7.85 (1H, d, J = 8.6 Hz), 8.17 (1H, s), 8.51 (1H, s).

ESI-MS (m/e): 326 (M+H)+.

Example 101



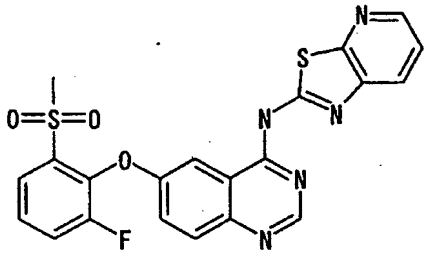
[6-(2,4-difluoro-6-(methylsulfonyl) phenoxy)-quinazoline-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine

The compound of Example 101 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 1,2,5-trifluoro-6-(methanesulphonyl) benzene, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR (DMSO-d6) δ : 3.69 (3H, s), 4.09 (3H, s), 7.02 (1H, d, J = 2.0 Hz), 7.97-7.99 (2H, m), 8.15-8.17 (2H, m), 8.33-8.36 (2H, m), 9.08 (1H, s).

ESI-MS (m/e): 432 (M+H)+.

Example 102



[6-(2-fluoro-6-(methylsulfonyl) phenoxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine

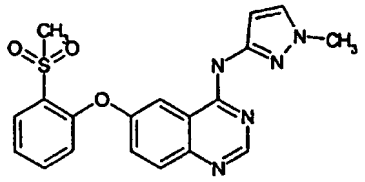
Into N,N-dimethylacetoamide solution (5 ml) of potassium tert-butoxide 120 mg (0.61 mmol) were added (6-hydroxy-quinazoline-4-yl)-thiazolo [5,4-b] pyridine-2-yl-amine 100 mg (0.34 mmol) and 1,2-difluoro-3-methanesulphonyl benzene 116 mg (0.61 mmol), and

thereafter, the mixture was stirred at room temperature for one hour. Water was added to the reaction liquor, and extraction was carried out with chloroform. The organic layer was dried and concentrated, thereafter the obtained residue was purified using thin layer silica gel chromatography (chloroform : methanol = 10 : 1) and the title compound 81 mg (yield: 51 %) was obtained as a yellow solid.

1H-NMR (DMSO-d6) δ : 3.41 (3H, s), 7.47-7.48 (1H, m), 7.67-7.69 (1H, m), 7.83-7.85 (1H, m), 7.92-7.97 (5H, m), 8.43-8.44 (1H, m), 8.87 (1H, s).

ESI-MS, (m/e): 468 (M+H) +.

Example 103



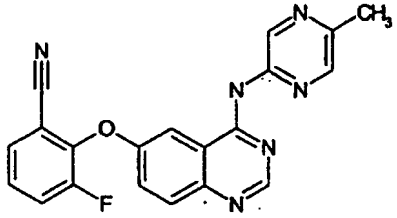
N-(1-methyl-1H-pyrazol-3-yl)-6-[2-(methylsulfonyl) phenoxy 1 quinazoline-4-yl-amine

The compound of Example 103 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2-methylsulfonyl fluorobenzene.

1H-NMR(CD3OD) δ : 3.39 (3H, s), 3.87 (3H, s), 6.70 (1H, s), 7.15 (1H, d, J = 8.2 Hz), 7.41 (1H, t, J = 7.6 Hz), 7.56 (1H, d, J = 2.0 Hz), 7.69-7.73 (2H, m), 7.88 (1H, d, J = 9.0 Hz), 8.07-8.10 (1H, m), 8.12 (1H, d, J = 2.0 Hz), 8.54 (1H, s).

ESI-MS (m/e): 396 (M+H).

Example 104

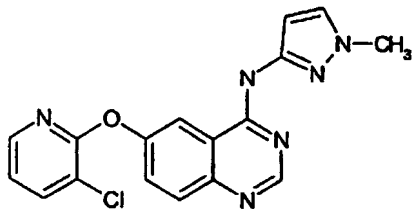


3-fluoro-2-({4-[(5-methylpyrazin-2-yl) amino] quinazolin-6-yl} oxy) benzonitrile.

The compound of Example 157 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2,3-difluoro benzonitrile, 2-amino-5-methylpyrazine and 4-chloro-6-hydroxy-quinazoline.

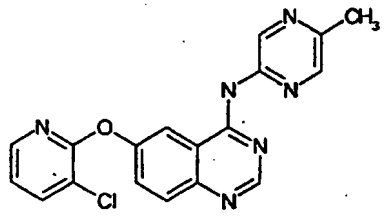
1H-NMR (DMSO-d6) δ : 2.49 (3H, s), 7.59-7.61 (1H, m), 7.87-7.97 (4H, m), 8.15 (1H, d, J = 2.4 Hz), 8.37-8.40,(1H, m), 8.76-8.79 (1H, m), 9.28 (1H, s).
ESI-MS (m/e): 373 (M+H)+.

Example 105



6-(3-chloropyridin-2-yl sulphanyl) (1-methylpyrazol-3-yl) quinazoline1104-yl-amine
4-[(1-methyl-1H-pyrazol-3-yl) amino] quinazolin-6-ol 80 mg (0.332 mmol) and 2-fluoro-3-methylbenzo nitrile 147 mg (0.993 mmol) were added to N,N-dimethylacetamide solution (7 ml) of sodium hydride (60 % contents) 33 mg (1.375 mmol), and thereafter, the mixture was stirred at 130°C for three hours. Water was added to the reaction liquor, and extraction was carried out with chloroform. The organic layer was dried and concentrated, thereafter the obtained residue was purified using silica gel chromatography (chloroform : methanol = 9 : 1), and the title compound 60 mg (yield: 51 %) was obtained as a colourless solid.
1H-NMR(CD3OD) δ : 3.88 (3H, s), 6.79 (1H, m), 7.09-7.12 (1H, m), 7.44 (1H, d, J = 2.4 Hz), 7.64 (1H, dd, J = 8.8, 2.4 Hz), 7.86-7.90 (2H, m), 8.04 (1H, dd, J = 4.8, 1.6 Hz), 8.07 (1H, d, J = 2.0 Hz), 8.59 (1H, brs).
ESI-MS (m/e): 353 (M+H)+.

Example 106

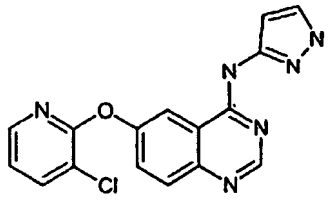


6-(3-chloropyridine-2-yl) sulphanyl-(5-methyl-pyrazine-2-yl) quinazoline-4-yl-amine
The compound of Example 106 was produced by the same method as in Example 95, a process based on this or a combination of these and a normal procedure using 2,3-dichloropyridine, 2-amino-5-methylpyrazine and 4-chloro-6-hydroxy-quinazoline.
1H-NMR(CD90D) δ : 2.58 (3H, s), 7.11-7.15 (1H, m), 7.43 (1H, d, J = 2.0 Hz), 7.69 (1H, dd, J = 8.0, 1.6 Hz), 7.73 (1H, dd, J = 8.8, 2.4 Hz), 7.91 (1H, dd, J = 8.0, 1.6 Hz), 7.97 (1H,

d, J = 8.8 Hz), 8.05 (1H, dd, J = 4-8,2.0 Hz), 8.16 (1H, d, J = 2.4 Hz), 8.27 (1H, s), 9.72 (1H, s).

ESI-MS (m/e): 365 (M+H)+.

Example 107



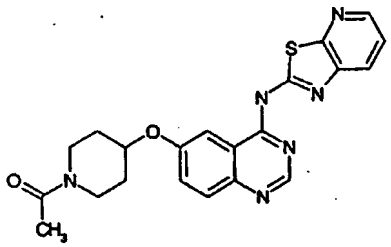
6-(3-chloropyridine-2-yl) sulphanyl-(1H-pyrazol-3-yl) quinazoline-4-yl-amine

The compound of Example 107 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2,3-dichloropyridine, 3-amino-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 7.12-7.16 (1H, m), 7.59 (1H, brs), 7.67 (1H, d, J = 8.8 Hz), 7.87 (1H, d, J = 8.8 Hz), 7.94 (1H, dd, J = 8.0, 1.6 Hz), 8.03 (1H, dd, J = 4.8, 1.6 Hz), 8.16 (1H, d, J = 2.0 Hz), 8.62 (1H, brs).

ESI-MS (m/e): 339 (M+H)+.

Example 108



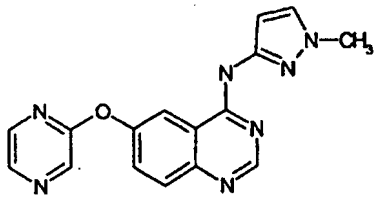
6-(acetyl piperidine-4-yl) oxy-N-[1,3] thiazolo [5,4-d] pyridin-2-yl quinazoline-4-yl-amine

The compound of Example 108 was produced by the same process as in Example 22, a process based on this or a combination of these and a normal procedure using 4-hydroxy-1-acetyl piperidine, thiazolo [5,4-b] pyridine-2-yl-amine and 4-chloro-6-hydroxy quinazoline.

1H-NMR(CD3OD) δ : 1.87-1.98 (2H, m), 2.05-2.19 (2H, m), 3.54-3.69 (2H, m), 3.79-4.68 (2H, m), 4.87-4.91 (1H, m), 7.41-7.44 (1H, m), 7.51 (1H, d, J = 8.0 Hz), 7.78 (1H, d, J = 8.0 Hz), 7.97 (1H, d, J = 2.4 Hz), 8.03 (1H, d, J = 7.2 Hz), 8.39 (1H, dd, J = 4.8, 1.2 Hz), 8.66 (1H, brs).

ESI-MS (m/e): 421 (M+H)+.

Example 109



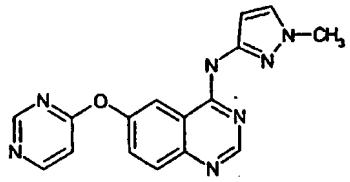
N-(1-methyl-1H-pyrazol-3-yl)-6-(pyrazine-2-yloxy) quinazoline-4-yl-amine

The compound of Example 109 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2-chloropyrazine, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy quinazoline.

1H-NMR(CD3OD) δ : 3.88 (3H, s), 6.83 (1H, d, J = 2.4 Hz), 7.46 (1H, d, J = 2.4 Hz), 7.67 (1H, dd, J = 8.8, 2.4 Hz), 7.91 (1H, d, J = 8.8 Hz), 8.13 (1H, d, J = 2.4 Hz), 8.17-8.18 (1H, m), 8.34 (1H, d, J = 2.8 Hz), 8.53 (1H, d, J = 1-2 Hz), 8.65 (1H, s).

ESI-MS (m/e): 320 (M+H)+.

Example 110



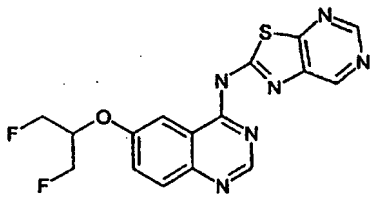
N-(1-methyl-1H-pyrazol-3-yl)-6-(pyrimidine-4-yloxy) quinazoline-4-yl-amine

The compound of Example 110 was produced by the same method as in Example 95, a process based on this or a combination of these and a normal procedure using 4-chloropyrimidine, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy quinazoline.

1H-NMR(CD3OD) δ : 3.88 (3H, s), 6.83 (1H, brs), 7.15 (1H, d, J = 5.2 Hz), 7.46 (1H, brs), 7.66 (1H, d, J = 8.8 Hz), 7.92 (1H, d, J = 8.8 Hz), 8.16 (1H, d, J = 2.4 Hz), 8.64-8.66 (2H, m), 8.75 (1H, s).

ESI-MS (m/e): 320 (M+H)+.

Example 111



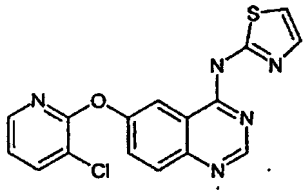
6-[2-fluoro-1-(fluoromethyl) ethoxy]-N-[1,3] thiazolo [5,4-d] pyrimidin-2-yl quinazoline-4-yl-amine

The compound of Example 111 was produced by the same process as in Example 22, a process based on this or a combination of these and a normal procedure using 2-fluoro-1-(fluoromethyl) ethanol, thiazolo [5,4-b] pyridine-2-yl-amine and 4-chloro-6-hydroxy quinazoline.

1H-NMR(CD3OD) δ : 4.71-4.82 (2H, m), 4.83-4.91 (2H, m), 5.05-5.14 (1H, m), 7.61-7.64 (1H, m), 7.07-7.10 (1H, m), 7.83 (1H, brs), 8.13 (1H, d, J = 2.4 Hz), 8.80 (1H, brs), 8.94 (1H, s), 9.04 (1H, s).

ESI-MS (m/e): 375 (M+H)+.

Example 112



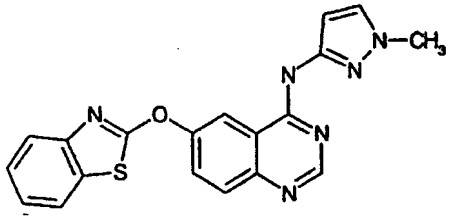
6-[(3-chloropyridine-2-yl) oxy]-N-1,3-thiazol-2-yl quinazoline-4-amine (1-methylpyrazol-3-yl) quinazoline-4-yl-amine

The compound of Example 112 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2,3-dichloropyridine, 2-amino-thiazole and 4-chloro-6-hydroxy quinazoline.

1H-NMR(CD3OD) δ : 7.08-7.13 (3H, m), 7.50 (1H, d, J = 2.8 Hz), 7.69-7.74 (1H, m), 7.90 (1H, dd, J = 6.0, 2.0 Hz), 7.91-7.94 (1H, m), 8.05 (1H, dd, J = 4.8, 2.0 Hz), 8.22 (1H, d, J = 2.8H, Z).

ESI-MS (m/e): 356 (M+H)+.

Example 113



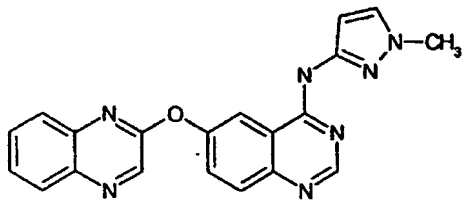
6-(1,3-benzothiazol-2-yloxy)-N-(1-methyl-1H-pyrazol-3-yl) quinazoline-4-yl-amine

The compound of Example 113 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2-chloro-1,3-benzothiazole, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy quinazoline.

1H-NMR(CD3OD) δ : 3.87 (3H, s), 6.86 (1H, d, J = 2.4 Hz), 7.34 (1H, t, J = 8.4 Hz), 7.41-7.46 (2H, m), 7.74 (1H, t, J = 8.4 Hz), 7.84 (1H, dd, J = 8.8, 2.8 Hz), 7.95 (1H, d, J = 8.8 Hz), 8.33 (1H, d, J = 2.8 Hz), 8.68 (1H, s).

ESI-MS (m/e): 375 (M+H)+.

Example 114



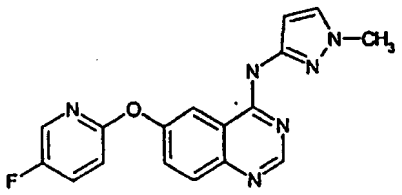
N-(1-methyl-1H-pyrazol-3-yl)-6-(quinazoline-2-yloxy) quinazoline-4-yl-amine

The compound of Example 114 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2-chloroquinazoline, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 3.86 (3H, s), 6.82 (1H, brs), 7.45 (1H, d, J = 2.4 Hz), 7.57-7.79 (3H, m), 7-90-7.95 (1H, m), 8.06-8.09 (1H, m), 8.24 (1H, d, J = 2.4 Hz), 8.65 (1H, brs), 8.78 (1H, s).

ESI-MS (m/e): 370 (M+H)+.

Example 115



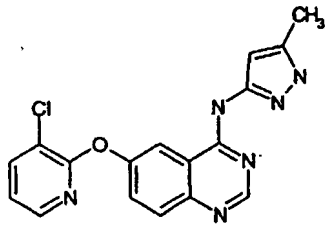
6-[(5-fluoropyridine-2-yl) oxy]-N-(1-methyl-1H-pyrazol-3-yl) quinazoline-4-yl-amine

The compound of Example 115 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2,5-difluoro pyridine, 3-amino-1-methylpyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 3.88 (3H, s), 6.78 (1H, d, J = 2.4 Hz), 7.10 (1H, dd, J = 8.8, 2.8 Hz), 7.48 (1H, d, J = 2.4 Hz), 7.62-7.66 (2H, m), 7.86 (1H, d, J = 8.-8 Hz), 8.03 (1H, d, J = 2.8 Hz), 8.06 (1H, d, J = 2.4 Hz), 8.61 (1H, s).

ESI-MS (m/e): 337 (M+H)+.

Example 116



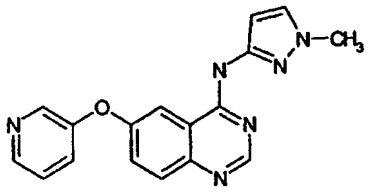
6-[(3-chloropyridine-2-yl) oxy]-N-(5-methyl-1H-pyrazol-3-yl) quinazoline-4-yl-amine

The compound of Example 116 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2,3-dichloropyridine, 3-amino-5-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 2.33 (3H, s), 7.09-7.12 (1H, m), 7.66 (1H, dd, J = 8.8, 2.4 Hz), 7.90 (1H, d, J = 8.8 Hz), 8.04 (1H, dd, J = 5.2, 2.0 Hz), 8.11 (1H, d, J = 2.4 Hz), 8.66 (1H, s).

ESI-MS (m/e): 353 (M+H)+.

Example 117



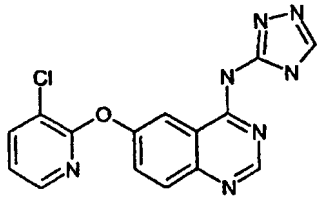
N-(1-methyl-1H-pyrazol-3-yl)-6-(pyridine-3-yloxy) quinazoline-4-yl-amine

The compound of Example 117 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 3-fluoropyridine, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 3.87 (3H, s), 6.85 (1H, d, J = 2.4 Hz), 7.42-7.47 (3H, m), 7.58 (1H, dd, J = 8.8, 2.8 Hz), 7.87-7.90 (2H, m), 8.39 (1H, dd, J = 4.4, 1.2 Hz), 8.43 (1H, d, J = 2.8 Hz), 8.64 (1H, s).

ESI-MS (m/e): 319 (M+H)+.

Example 118



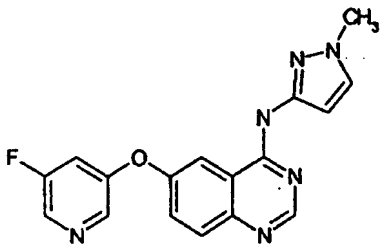
6-[(3-chloropyridine-2-yl) oxy]-N-4H-[1,2,4]-triazol-3-yl quinazoline-4-yl-amine

The compound of Example 118 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2,3-dichloropyridine, 3-amino-4H-[1,2,4] triazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 7.10-7.13 (1H, m), 7.69 (2H, br), 7.88 (2H, br), 7.90 (1H, dd, J = 7.6, 1.6 Hz), 8.05 (1H, dd, J = 4.8, 1.6 Hz), 8.22 (1H, d, J = 2.4 Hz).

ESI-MS (m/e): 340 (M+H)+.

Example 119



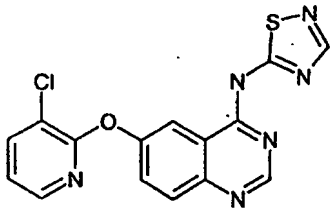
6-[(5-fluoropyridine-3-yl) oxy]-N-(1-methyl-1H-pyrazol-3-yl) quinazoline-4-yl-amine

The compound of Example 119 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 3,5-difluoro pyridine, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 3.87 (1H, s), 6.74 (1H, d, J = 2.4 Hz), 7.32-7.36 (1H, m), 7.51 (1H, d, J = 2.0 Hz), 7.66 (1H, dd, J = 8.8, 2.4 Hz), 7.90 (1H, d, J = 8.8 Hz), 8.05 (1H, d, J = 2.4 Hz), 8.29-8.30 (2H, m), 8.59 (1H, s).

ESI-MS (m/e): 337 (M+H)+.

Example 120



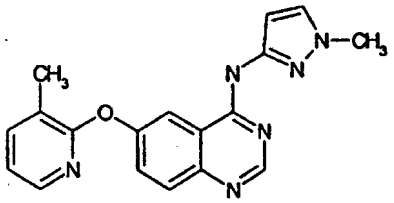
6-[(3-chloropyridine-2-yl) oxy]-N-[1,2,4]-thiadiazol-5-yl quinazoline-4-yl-amine

The compound of Example 120 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2,3-dichloropyridine, 3-amino-[1,2,4] thiadiazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 7.14-7.18 (1H, m), 7.74-7.77 (1H, m), 7.93-7.96 (1H, m), 8.00 (1H, d, J = 8.4 Hz), 8.05-8.06 (1H, m), 8.33-8.34 (1H, m), 8.36 (1H, d, J = 1.6 Hz), 8.91 (1H, d, J = 1.2 Hz).

ESI-MS (m/e): 357[M+H]+.

Example 121



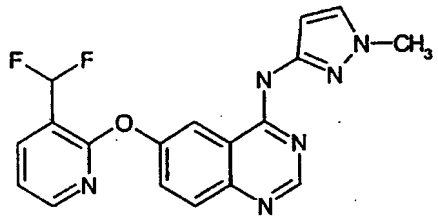
N-(1-methyl-1H-pyrazole-3-yl)-6-[(3-methylpyridine-2-yl) oxy] quinazoline-4-yl-amine

The compound of Example 121 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2-chloro-3-methylpyridine, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 2.42 (3H, s), 3.87 (3H, s), 6.82 (1H, d, J = 2.4 Hz), 7.04-7.08 (1H, m), 7.46 (1H, d, J = 2.4 Hz), 7.61 (1H, dd, J = 8.8, 2.4 Hz), 7.68 (1H, dd, J = 7.2, 1.6 Hz), 7.87 (1H, d, J = 8.8 Hz), 7.96-7.99 (2H, m), 8.61 (1H, s).

ESI-MS (m/e): 333 (M+H)+.

Example 122



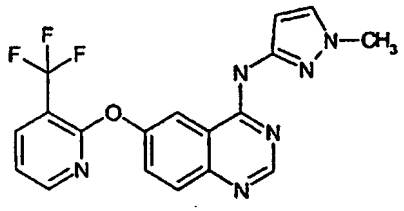
6-{[3-(difluoromethyl) pyridin-2-yl] oxy}-N-(1-methyl-1H-pyrazol-3-yl) quinazoline-4-yl-amine

The compound of Example 122 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2-chloro-3-(difluoromethyl) pyridine, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 3.86 (3H, s), 6.88 (1H, d, J = 2.0 Hz), 7.11 (1H, t, J = 55 Hz), 7.20-7.24 (1H, m), 7.42 (1H, d, J = 2.0 Hz), 7.65 (1H, dd, J = 8.8, 2.4 Hz), 7.90 (1H, d, J = 8.8 Hz), 8.06-8.09 (2H, m), 8.22-8.24 (1H, m), 8.66 (1H, s).

ESI-MS (m/e): 369 (M+H)+.

Example 123



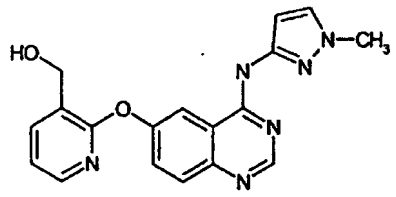
N-(1-methyl-1H-pyrazol-3-yl)-6-{[3-(trifluoromethyl) pyridin-2-yl] oxy} quinazoline-4-yl-amine

The compound of Example 123 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2-chloro-3-(trifluoromethyl) pyridine, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 3.87 (3H, s), 6.89 (1H, brs), 7.21-7.24 (1H, m), 7.42 (1H, brs), 7.66 (1H, d, J = 8.8 Hz), 7.90 (1H, d, J = 8.8 Hz), 8.07-8.11 (2H, m), 8.30 (1H, d, J = 3.6 Hz), 8.67 (1H, s).

ESI-MS (m/e): 387 (M+H)+.

Example 124



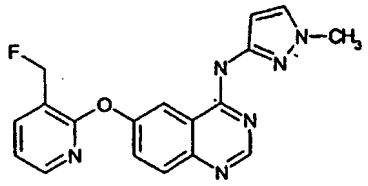
[2-({4-[[1-methyl-1H-pyrazol-3-yl] amino] quinazolin-6-yl} oxy) pyridin-3-yl] methanol

The compound of Example 124 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2-chloro-3-hydroxymethyl pyridine, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CDBOD) δ : 3.87 (3H, s), 4.85 (2H, s), 6.81 (1H, d, J = 2.4 Hz), 7.13-7.16 (1H, m), 7.44 (1H, d, J = 2.4 Hz), 7.63 (1H, dd, J = 8.0, 2.0 Hz), 7.86 (1H, d, J = 8.8 Hz), 7.96 (1H, dd, J = 6.4, 2.0 Hz), 8.01 (1H, d, J = 2.0 Hz), 8.03 (1H, dd, J = 4.8, 2.0 Hz), 8.62 (1H, s).

ESI-MS (m/e): 349 (M+H)+.

Example 125



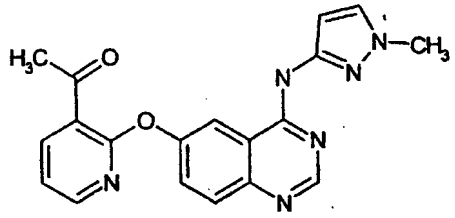
6-{[3-(fluoromethyl) pyridin-2-yl] oxy}-N-(1-methyl-1H-pyrazol-3-yl) quinazoline-4-yl-amine

The compound of Example 125 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2-chloro-3-fluoromethyl pyridine, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 3.87 (1H, s), 5.64 (2H, d, J = 47 Hz), 6.84 (1H, d, J = 2.4 Hz), 7.16-7.19 (1H, m), 7.45 (1H, d, J = 2.4 Hz), 7.65 (1H, dd, J = 8.8, 2.8 Hz), 7.88 (1H, d, J = 8.8 Hz), 7.93 (1H, d, J = 6.4 Hz), 8.05 (1H, d, J = 2.0 Hz), 8.13 (1H, d, J = 4.8 Hz), 8.64 (1H, s).

ESI-MS (m/e): 351 (M+H)+.

Example 126



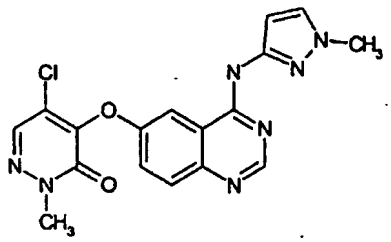
1-[2-({4-[[1-methyl-1H-pyrazol-3-yl] amino] quinazolin-6-yl} oxy) pyridine 3-yl] ethanone

The compound of Example 126 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 3-acetyl-2-chloropyridine, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 2.83 (3H, s), 3.88 (3H, s), 6.87 (1H, br), 7.20-7.24 (1H, m), 7.43 (1H, d, J = 2.4 Hz), 7.65 (1H, d, J = 8.8 Hz), 7.90 (1H, d, J = 8.8 Hz), 8.10 (1H, d, J = 2.4 Hz), 8.26-8.30 (2H, m), 8.63 (1H, s).

ESI-MS (m/e): 361 (M+H)+.

Example 127



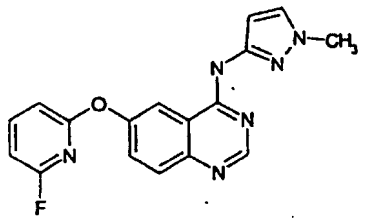
5-chloro-2-methyl-4-({4-[[1-methyl-1H-pyrazol-3-yl] amino] quinazolin-6-yl} oxy) pyridazine-3 (2H)-on

The compound of Example 127 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 4,5-dichloro-2-methyl-3 (2H) pyridazinone, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 3.82 (3H, s), 3.87 (3H, s), 6.83 (1H, d, J = 2.4 Hz), 7.44 (1H, d, J = 2.4 Hz), 7.61 (1H, dd, J = 8.8, 2.4 Hz), 7.71 (1H, d, J = 2.4 Hz), 7.85 (1H, d, J = 8.8 Hz), 7.99 (1H, s), 8.60 (1H, s).

ESI-MS (m/e): 384 (M+H)+.

Example 128



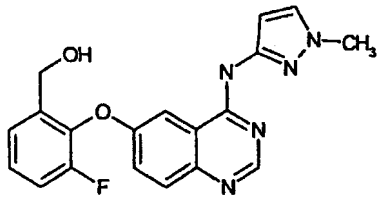
6-[(6-fluoropyridine-2-yl) oxy]-N-(1-methyl-1H-pyrazol-3-yl) quinazoline-4-yl-amine

The compound of Example 128 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2,6-difluoro pyridine, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 3.89 (3H, s), 6.74 (1H, dd, J = 8.0, 2.4 Hz), 6.79 (1H, d, J = 2.4 Hz), 6.91 (1H, d, J = 8.0 Hz), 7.47 (1H, d, J = 2.4 Hz), 7.68 (1H, dd, J = 8.8, 2.0 Hz), 7.88 (1H, d, J = 8.8 Hz), 7.89-7.96 (1H, s), 8.15 (1H, d, J = 2.8 Hz), 8.62 (1H, s).

ESI-MS (m/e): 337 (M+H)+.

Example 129



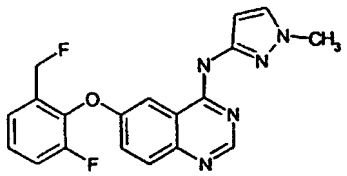
[3-fluoro-2-({4-[[1-methyl-1H-pyrazol-3-yl] amino] quinazolin-6-yl} oxy) phenyl] methanol.

The compound of Example 129 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2,3-difluorobenzene methanol, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 3.85 (3H, s), 4.72 (2H, s), 6.75 (1H, br), 7.14-7.19 (1H, m), 7.27-7.33 (1H, m), 7.69 (1H, dd, J = 8.0, 1.6 Hz), 7.85 (1H, d, J = 8.8 Hz), 7.41-7.44 (2H, m), 7.56 (2H, br), 7.79 (1H, br), 8.55 (1H, s).

ESI-MS (m/e): 366 (M+H)+.

Example 130



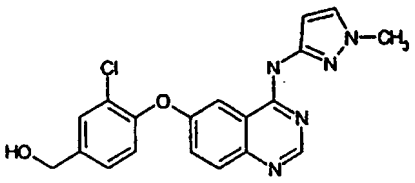
6-[2-fluoro-6-(fluoromethyl) phenoxy]-N-(1-methyl-1H-pyrazol-3-yl) quinazoline-4-yl-amine

The compound of Example 130 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 1,2-difluoro-3-(fluoromethyl) benzene, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 3.85 (3H, s), 5.47 (2H, d, J = 47 Hz), 6.82 (1H, d, J = 2.4 Hz), 7.25-7.42 (4H, m), 7.52 (1H, dd, J = 8.8, 2.4 Hz), 7.59 (1H, d, J = 2.4 Hz), 7.82 (1H, d, J = 8.8 Hz), 8.59 (1H, s).

ESI-MS (m/e): 368 (M+H)+.

Example 131



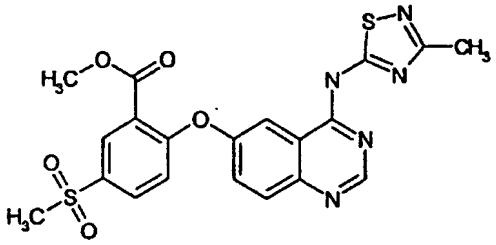
[3-chloro-4-({4-[[1-methyl-1H-pyrazol-3-yl] amino] quinazolin-6-yl} oxy) phenyl] methanol

The compound of Example 131 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 4-fluoro-3-chlorobenzene methanol, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 3.87 (3H, s), 4.67 (2H, s), 6.80 (1H, br), 7.13 (1H, d, J = 8.8 Hz), 7.42 (1H, d, J = 2.4 Hz), 7.52 (1H, d, J = 8.0 Hz), 7.55 (1H, d, J = 2.4 Hz), 7.66 (1H, br), 7.83 (1H, d, J = 8.4 Hz), 8.58 (1H, s)I.

ESI-MS (m/e): 382 (M+H)+.

Example 132



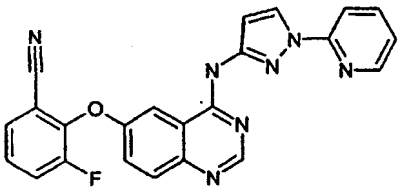
Methyl-5-(methylsulfonyl)-2-({4-[[3-methyl-[1,2,4]-thiadiazol-5-yl] amino] quinazolin-6-yl} oxy) benzoate

The compound of Example 132 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2-fluoro-5-methylsulfonyl-benzoic acid methyl ester, 5-amino-3-methyl-[1,2,4] thiadiazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 2.55 (3H, s), 3.19 (3H, s), 3.91 (3H, s), 7.25 (1H, d, J = 8.8 Hz), 7.72 (1H, dd, J = 8.8, 2.4 Hz), 8.03 (1H, d, J = 2.8 Hz), 8.05 (1H, d, J = 8.8 Hz), 8.11 (1H, dd, J = 8.8, 2.8 Hz), 8.58 (1H, d, J = 2.4 Hz), 8.95 (1H, s).

ESI-MS (m/e): 472 (M+H)+.

Example 133



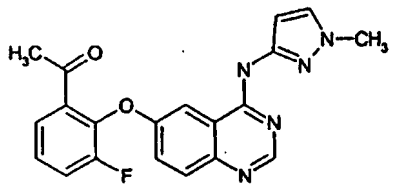
3-fluoro-2-({4-[[1-pyridine-2-yl-1H-pyrazol-3-yl] amino] quinazolin-6-yl} oxy) benzonitrile

The compound of Example 133 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2,3-difluoro benzonitrile, 3-amino-1-(pyridine-2-yl)-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 7.23-7.26 (2H, m), 7.47-7.51 (1H, m), 7.43 (1H, d, J = 2.0 Hz), 7.69 (1H, dd, 8.0, 1.6 Hz), 7.60-7.67 (4H, m), 7.84-7.90 (2H, s), 7.93 (1H, d, J = 2.8 Hz), 8.41 (1H, d, J = 5.2 Hz), 8.52 (1H, d, J = 2.8 Hz), 8.66 (1H, s).

ESI-MS (m/e): 424 (M+H)+.

Example 134



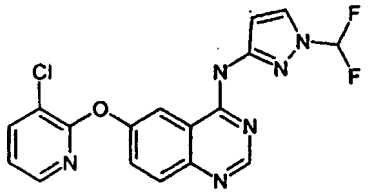
1-[3-fluoro-2-({4-[[1-methyl-1H-pyrazol-3-yl] amino] quinazolin-6-yl} oxy) phenyl] ethanone

The compound of Example 134 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 1-(2,3-difluorophenyl) ethanone, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 2.60 (3H, s), 3.85 (3H, s), 6.85 (1H, d, J = 2.4 Hz), 7.37-7.43 (3H, m), 7.55 (1H, dd, J = 8.8, 2.8 Hz), 7.61 (1H, d, J = 2.8 Hz), 7.69-7.71 (1H, m), 7.86 (1H, d, J = 8.8 Hz), 8.61 (1H, s).

ESI-MS (m/e): 378 (M+H)+.

Example 135



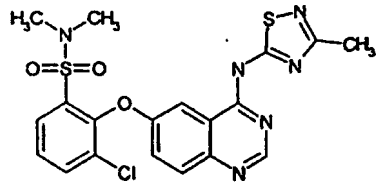
6-[(3-chloropyridine-2-yl) oxy]-N-[1-(difluoromethyl)-1H-pyrazol-3-yl] quinazoline-4-yl-amine

The compound of Example 135 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2,3-dichloropyridine, 3-amino-1-(difluoromethyl)-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD300) δ : 7.12-7.15 (1H, m), 7.21 (1H, d, J = 2.8 Hz), 7.31 (1H, t, J = 60 Hz), 7.70 (1H, dd, J = 8.8, 2.4 Hz), 7.90-7.94 (3H, m), 8.04 (1H, dd, J = 4.8, 1.6 Hz), 8.17 (1H, d, J = 2.4 Hz), 8.68 (1H, s).

ESI-MS (m/e): 389 (M+H)+.

Example 136



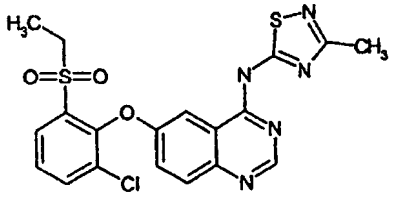
3-chloro-N,N-dimethyl-2-({4-[[3-methyl-[1,2,4]-thiadiazol-5-yl] amino] quinazolin-6-yl} oxy) benzenesulphon amide.

The compound of Example 136 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2,3-dichloro-N,N-dimethyl-benzenesulphon amide, 5-amino-3-methyl-[1,2,4] thiadiazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 2.54 (3H, s), 2.92 (6H, s), 7.53 (1H, t, J = 8.0 Hz), 7.62 (1H, dd, J = 8.8, 2.8 Hz), 7.76 (1H, d, J = 2.8 Hz), 7.80 (1H, dd, J = 8.0, 1.6 Hz), 8.00 (1H, d, J = 8.8 Hz), 8.02 (1H, dd, J = 8.0, 1.2 Hz), 8.89 (1H, s).

ESI-MS (m/e): 477 (M+H)+.

Example 137



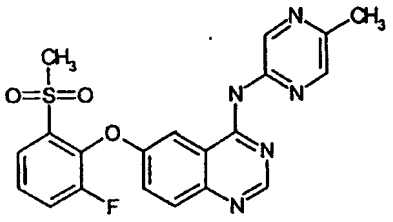
6-[2-chloro-6-(ethylsulfonyl) phenoxy]-N-(3-methyl-1,2,4-thiadiazol-5-yl) quinazoline-4-yl-amine

The compound of Example 137 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 1,2-dichloro-3-(ethane sulfonyl) benzene, 5-amino-3-methyl-[1,2,4] thiadiazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 1.34 (3H, t, J = 7.2 Hz), 2.54 (3H, s), 3.47 (2H, q, J = 7.2 Hz), 7.56 (1H, t, J = 8.0 Hz), 7.65 (1H, dd, J= 8.8, 2.4 Hz), 7.71 (1H, d, J = 2.4 Hz), 7.86 (1H, dd, J = 8.0, 1.6 Hz), 7.98 (1H, d, J = 8.8 Hz), 8.09 (1H, dd, J = 8.0, 1.6 Hz), 8.89 (1H, s).

ESI-MS (m/e): 356 (M+H)+.

Example 138



6-[2-fluoro-6-(methylsulfonyl) phenoxy]-N-(5-methylpyrazine-2-yl) quinazoline-4-yl-amine

5-methylpyrazine-2-amine 1.70 g (15.6 mmol), 2,2-bis diphenylphosphino-1,1-binaphthyl 0.37 g (0.6 mmol), cesium carbonate 7.80 g (24.0 mmol) and tris dibenzylideneacetone palladium were added to toluene solution (150 ml) of 4-chloro-6-acetate-quinazoline 2.70 g (12.0 mmol), and thereafter the mixture was stirred at 111°C for 18 hours. The reaction liquor was separated by filtration, water was added to filtrate, and extraction was carried out with chloroform. After drying and concentrating the organic layer, ammonia water 10 ml was added to the solution obtained by adding tetrahydrofuran 100 ml and methanol 100 ml to the obtained residue, and the mixture was stirred for 30 minutes. The reaction solution was concentrated, and thereafter the obtained residue was stirred over night with methanol

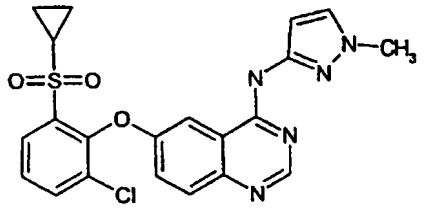
solution, and thereafter the reaction solution was separated by filtration, and the residue was dried, and 6-hydroxy-N-(5-methylpyrazine-2-yl) quinazoline-4-yl-amine 1.30 g (yield: 42 %) was obtained as a yellow solid.

The obtained hydroxy body 50 mg (0.20 mmol) and 1,2-difluoro-3-methanesulphonyl benzene 94 mg (0.50 mmol) were added to N,N-dimethylacetamide solution (3 ml) of potassium tert-butoxide 57 mg (0.50 mmol), and thereafter the mixture was stirred at 77°C for four hours. Water was added to the reaction liquor, and extraction was carried out with chloroform. The organic layer was dried and concentrated, thereafter the obtained residue was purified using reverse phase separation HPLC (0.1 % TFA-containing water : acetonitrile = 90 : 10 to 10 : 90), and the title compound 24 mg (yield: 29 %) was obtained as a yellow solid.

1H-NMR(CD3OD) δ : 2.56 (3H, s), 3.34 (3H, s), 7.54-7.70 (3H, m), 7.90-7.95 (3H, m), 8.27 (1H, s), 8.70 (1H, s), 9.61 (1H, s).

ESI-MS (m/e): 426 (M+H)+.

Example 139



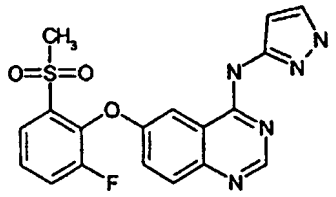
6-[2-chloro-6-(cyclopropyl sulfonyl) phenoxy]-N-(1-methyl-1H-pyrazol-3-yl) quinazoline-4-yl-amine

The compound of Example 139 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 1,2-dichloro-3-(cyclopropyl sulfonyl) benzene, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 1.10-1.13 (2H, m), 1.28-1.31 (2H, m), 2.97-3.03 (1H, m), 3.85 (3H, s), 6.71 (1H, br), 7.47-7.55 (3H, m), 7.68 (1H, brs), 7.84-7.87 (2H, m), 7.98 (1H, dd, J = 8.8, 1.6 Hz), 8.54 (1H, s).

ESI-MS (m/e): 456 (M+H)+.

Example 140



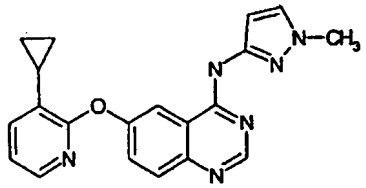
6-[2-fluoro-6-(methylsulfonyl) phenoxy]-N-1H-pyrazol-3-yl quinazoline-4-yl-amine

The compound of Example 140 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 1,2-difluoro-3-(methylsulfonyl) benzene, 3-amino-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 3.35 (3H, s), 7.48-7.58 (4H, m), 7.61 (1H, d, J = 8.8 Hz), 7.77 (1H, brs), 7.87 (1H, d, J = 8.8 Hz), 7.93 (1H, d, J = 7.6 Hz), 8.65 (1H, s).

ESI-MS (m/e): 400 (M+H)+.

Example 141



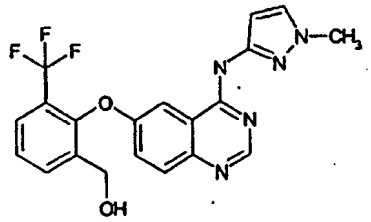
6-[3-cyclopropyl pyridin-2-yl] oxy]-N-(1-methyl-1H-pyrazol-3-yl) quinazoline-4-yl-amine

The compound of Example 141 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 3-cyclopropyl-2-chloropyridine, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 0.79-0.89 (2H, m), 1.03-1.08 (2H, m), 2.21-2.25 (1H, m), 3.88 (3H, s), 6.77 (1H, brs), 7.06-7.09 (1H, m), 7.43 (1H, dd, J = 7.4, 1.6 Hz), 7.49 (1H, brs), 7.63 (1H, d, J = 8.4 Hz), 7.86 (1H, d, J = 8.4 Hz), 7.93 (1H, dd, J = 4.8, 1.6 Hz), 8.04 (1H, d, J = 2.4 Hz), 8.59 (1H, s).

ESI-MS (m/e): 359 (M+H)+.

Example 142



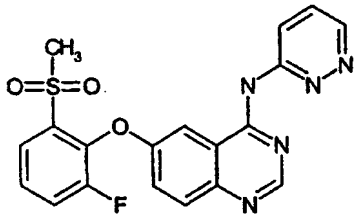
[2-({4-[[1-methyl-1H-pyrazol-3-yl] amino] quinazoline-6.-yl} oxy)-3-(trifluoromethyl) phenyl] methanol.

The compound of Example 142 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2-fluoro-3-(trifluoromethyl)-benzene methanol, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 3.85 (3H, s), 4.53 (2H, s), 6.77 (1H, d, J = 2.4 Hz), 7.41-7.52 (4H, m), 7.72 (1H, d, J = 7.6 Hz), 7.80 (1H, d, J = 8.8 Hz), 7.93 (1H, d, J = 7.6 Hz), 8.56 (1H, s).

ESI-MS (m/e):.416 (M+H)+.

Example 143



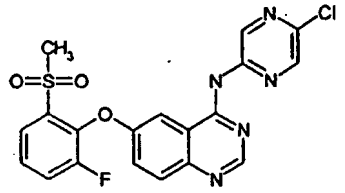
6-[2-fluoro-6-(methylsulfonyl) phenoxy]-N-pyridazin-3-yl quinazoline-4-yl-amine

The compound of Example 143 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 1,2-difluoro-3-(methylsulfonyl) benzene, 3-amino-pyridazine and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 3.37 (3H, s), 7.51-7.66 (4H, m), 7.90 (1H, d, J = 8-8 Hz), 7.94-7.96 (3H, m), 8.64 (1H, br), 8.84 (1H, s).

ESI-MS (m/e): 412 (M+H)+.

Example 144



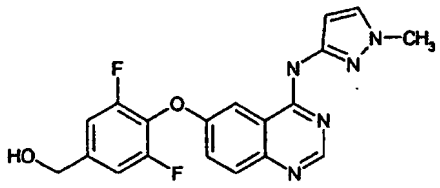
N-(5-chloropyrazine-2-yl)-6-[2-fluoro-6-(methylsulfonyl) phenoxy] quinazoline-4-yl-amine

The compound of Example 144 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 1,2-difluoro-3-(methylsulfonyl) benzene, 2-amino-5-chloropyrazine and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 3.37 (3H, s), 7.54-7.60 (2H, m), 7.71 (1H, dd, J = 8.8, 2.8 Hz), 7.80, (1H, d, J = 2.8 Hz), 7.95 (1H, s), 7.96 (1H, d, J = 8.8 Hz), 8.29 (1H, s), 8.79 (1H, s), 9.84 (1H, s).

ESI-MS (m/e): 446 (M+H)+.

Example 145



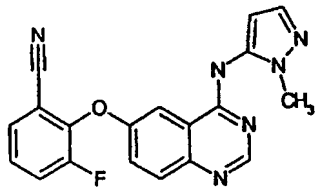
[3,5-difluoro-4-({4-[[1-methyl-1H-pyrazol-3-yl] amino] quinazolin-6-yl} oxy) phenyl] methanol

The compound of Example 145 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 3,4,5-trifluoro-benzene methanol, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 3.83 (3H, s), 4.65 (2H, s), 6.80 (1H, d, J = 2.0 Hz), 7.07-7.09 (2H, m), 7.42 (1H, d, J = 2.0 Hz), 7.57 (1H, dd, J = 8.8, 2.0 Hz), 7.67 (1H, d, J = 2.4 Hz), 7.83 (1H, d, J = 8.8 Hz), 8.59 (1H, s).

ESI-MS (m/e): 384 (M+H)+.

Example 146



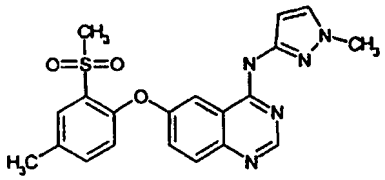
3-fluoro-2-({4-[[1-methyl-1H-pyrazol-5-yl] amino] quinazolin-6-yl} oxy) benzonitrile

The compound of Example 146 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2,3-difluoro benzonitrile, 5-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 3.70 (3H, s), 7.38-7.44 (1H, m), 7.53-7.60 (3H, m), 7.66-7.69 (3H, m), 8.00 (1H, d, J = 9.2 Hz), 9.00 (1H, s).

ESI-MS (m/e): 361 (M+H)+.

Example 147



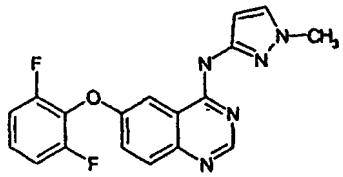
6-[4-methyl-2-(methylsulfonyl) phenoxy]-N-(1-methyl-1H-pyrazole-3-yl) quinazoline-4-yl-amine

The compound of Example 147 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 1-fluoro-4-methyl-2-(methylsulfonyl) benzene, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 2.46 (3H, s), 3.87 (3H, s), 6.75 (1H, brs), 7.00 (1H, d, J = 8.8 Hz), 7.49 (1H, brs), 7.65 (1H, s), 7.87 (1H, d, J = 8.8 Hz), 7.88 (1H, s), 7.99 (1H, brs), 8.59 (1H, s).

ESI-MS (m/e): 410 (M+H)+.

Example 148



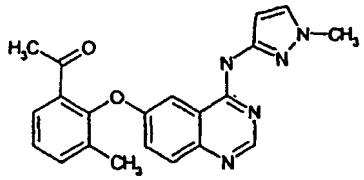
6-(2,6-difluoro phenoxy)-N-(1-methyl-pyrazol-3-yl) quinazoline-4-yl-amine

The compound of Example 148 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 1,2,3-trifluorobenzene, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR (CDCl3) δ : 3.80 (3H, s), 7.03 (2H, t, J = 8.4 Hz), 7.14-7.17 (1H, m), 7.33 (1H, br), 7-50-7.61 (1H, m), 7.91-7.94.(2H, m), 8.02 (1H, brs), 8.75 (1H, s).

ESI-MS (m/e): 354 (M+H)+.

Example 149



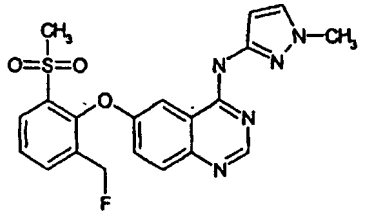
1-[3-methyl-2-([4-[[1-methyl-pyrazol-3-yl] amino] quinazolin-6-yl] oxy) phenyl] ethanone

4-[(1-methyl-1H-pyrazol-3-yl) amino] quinazolin-6-ol 71 mg (0.295 mmol) and 1-(2-fluoro-3 methylphenyl) ethanone 90 mg (0.592 mmol) were added to N,N-dimethylacetamide solution (5 ml) of potassium t-butoxide 82 mg (0.732 mmol), and thereafter the mixture was stirred at 130°C for five hours. Water was added to the reaction liquor, and extraction was carried out with chloroform. The organic layer was dried and concentrated, thereafter the obtained residue was purified using silica gel chromatography (chloroform : methanol = 12 : 1) and the title compound 6 mg (yield: 5 %) was obtained as a colourless solid.

1H-NMR(CD3OD) δ : 2.16 (3H, s), 2.54 (3H, s), 3.83 (3H, s), 6.90 (1H, br), 7.16 (1H, br), 7.33-7.35 (2H, m), 7.45-7.53 (2H, m), 7.70 (1H, d, J = 6.8 Hz), 7.86 (1H, d, J = 8.8 Hz), 8.64 (1H, s).

ESI-MS (m/e): 374 (M+H)+.

Example 150



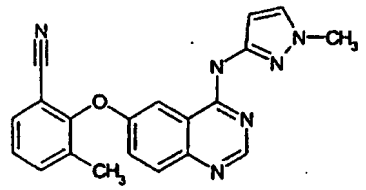
6-[2-(fluoromethyl)-6-(methylsulfonyl) phenoxy]-N-(1-methyl-pyrazole-3-yl) quinazoline-4-yl-amine

The compound of Example 150 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2-fluoro-1-(fluoromethyl)-3-(methylsulfonyl) benzene, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 3.30 (3H, s), 3.82 (3H, s), 5.23 (2H, d, J = 47 Hz), 6.88 (1H, d, J = 2.0 Hz), 7.43 (1H, d, J = 2.0 Hz), 7.51 (1H, dd, J = 8.8, 3.2 Hz), 7.60 (1H, d, J = 8.0 Hz), 7.86-7.91 (3H, m), 8.16 (1H, d, J = 7.2 Hz), 8.64 (1H, s).

ESI-MS (m/e): 428 (M+H)+.

Example 151



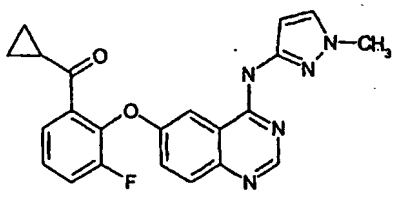
3-methyl-2-({4-[[1-methyl-pyrazol-3-yl] amino] quinazolin-6-yl} oxy) benzonitrile

4-[(1-methyl-1H-pyrazol-3-yl) amino] quinazolin-6-ol 90 mg (0.373 mmol) and 2-fluoro-3-methylbenzo nitrile 100 mg (0.741 mmol) were added to N,N-dimethylacetamide solution (5 ml) of potassium t-butoxide 105 mg (0.937 mmol) and thereafter, the mixture was stirred at 110°C for four hours. Water was added to the reaction liquor, and extraction was carried out with chloroform. The organic layer was dried and concentrated, thereafter the obtained residue was purified using silica gel chromatography (chloroform : methanol = 12 : 1), and the title compound 31 mg (yield: 23 %) was obtained as a colourless solid.

1H-NMR(CD3OD) δ : 2.20 (3H, s), 3.82 (3H, s), 6.80 (1H, brs), 7.28-7.33 (1H, m), 7.43-7.45 (2H, m), 7.56-7.60 (3H, m), 7.81 (1H, d, J = 8.4 Hz), 8.55 (1H, brs).

ESI-MS (m/e): 357 (M+H)+.

Example 152



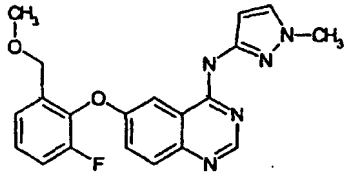
Cyclopropyl [3-fluoro-2-([4-[{1-methyl-pyrazol-3-yl} amino] quinazolin-6-yl] oxy) phenyl] methanone

4-[(1-methyl-1H-pyrazol-3-yl) amino] quinazolin-6-ol 70 mg (0.290 mmol) and cyclopropyl (2,3-difluorophenyl) methanone 63 mg (0.346 mmol) were added to N,N-dimethylacetamide solution (6 ml) of potassium t-butoxide 81 mg (0.723 mmol) and thereafter, the mixture was stirred at 110°C for one hour. Water was added to the reaction liquor, and extraction was carried out with chloroform. The organic layer was dried and concentrated, thereafter the obtained residue was purified using silica gel chromatography (chloroform : methanol = 10 : 1), and the title compound 36 mg (yield: 31 %) was obtained as a colourless solid.

1H-NMR(CD3OD) δ : 0.95-1.00 (2H, m), 1.14-1.18 (2H, m), 2.55-2.59 (1H, m), 3.84 (3H, s), 6.92 (1H, brs), 7.33-7.57 (6H, m), 7.87 (1H, d, J = 8.8 Hz), 8.66 (1H, s).

ESI-MS (m/e): 404 (M+H)+.

Example 153



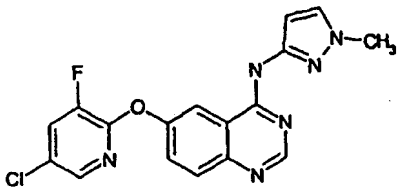
6-[2-fluoro-6-(methoxymethyl) phenoxy]-N-(1-methyl-pyrazol-3-yl) quinazoline-4-yl-amine

The compound of Example 153 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 1,2-difluoro-3-(methoxymethyl) benzene, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 3.34 (3H, s), 3.82 (3H, s), 6.95 (1H, brs), 7.12-7.17 (2H, m), 7.22-7.27 (1H, m), 7.31-7.34 (1H, m), 7.53 (1H, brs), 7.87 (1H, brs), 8.08 (1H, brs), 8.72 (1H, s).

ESI-MS (m/e): 380 (M+H)+.

Example 154



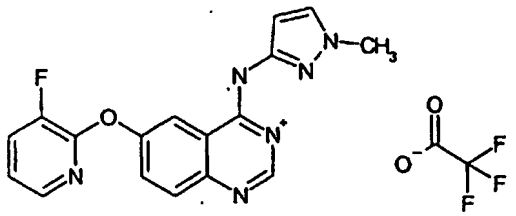
[6-(5-chloro-3-fluoropyridine-2-yloxy)-quinazoline-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine

The compound of Example 154 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2,5-dichloro-3-fluoropyridine, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR (DMSO-d6) δ : 3.81 (3H, s), 6.79 (1H, d, J = 2.4 Hz), 7.69 (1H, d, J = 2.4 Hz), 7.81 (1H, dd, J = 8-8,2.4 Hz), 7.86 (1H, d, J = 8.8 Hz), 8.13 (1H, d, J = 2.4 Hz), 8.33 (1H, dd, J = 8.8, 2.4 Hz), 8.51 (1H, d, J = 2-4 Hz), 8.70 (1H, s).

ESI-MS (m/e): 371 (M+H)+.

Example 155



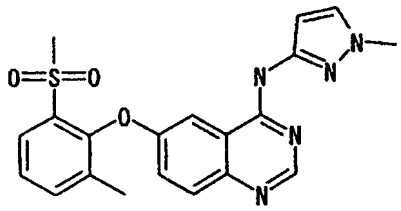
[6-(3-fluoropyridine-2-yloxy)-quinazoline-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine

The compound of Example 155 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2-chloro-3-fluoropyridine, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR (CDCl3) δ : 3.86 (3H, s), 6.93 (1H, d, J = 2.3 Hz), 7.09-7.13 (1H, m), 7.39 (1H, d, J = 2.3 Hz), 7.54-7.59 (1H, m), 7.76 (1H, dd, J = 9.0, 2.3 Hz), 7.91-7.92 (1H, m), 8.10 (1H, d, J = 9.0 Hz), 8.15 (1H, d, J = 2.3 Hz), 8.79 (1H, s).

ESI-MS (m/e): 337 (M+H)+.

Example 156



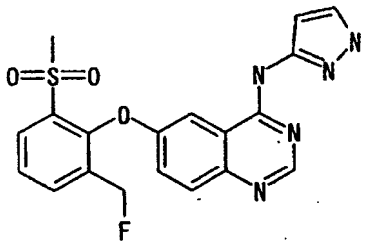
6-[2-methyl-6-(methylsulfonyl) phenoxy]-N-(1-methyl-pyrazol-3-yl) quinazoline-4-yl-amine

The compound of Example 156 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2-fluoro-1-methyl-3-(methylsulfonyl) benzene, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR (CDCl3) δ : 2.09 (3H, s), 3.26 (3H, s), 3.81 (3H, s), 6.88-7.00 (1H, br), 7.02-7.12 (1H, br), 7.31 (1H, d, J = 2.0 Hz), 7.38 (1H, t, J = 8.0 Hz), 7.46-7.54 (1H, br), 7.55 (1H, d, J = 8.0 Hz), 7.82-7.96 (1H, br), 7.98 (1H, d, J = 8.0 Hz), 8.00-8.12 (1H, br).

ESI-MS (m/e): 409 (M+H)+.

Example 157



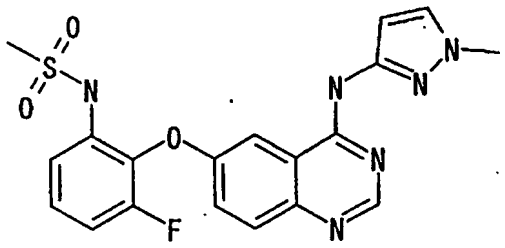
6-[2-(fluoromethyl)-6-(methylsulfonyl) phenoxy]-N-(1H-pyrazol-3-yl) quinazoline-4-yl-amine

The compound of Example 157 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2-fluoro-1-(fluoromethyl)-3-(methylsulfonyl) benzene, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 3.34 (3H, s), 5.33 (2H, d, J = 47 Hz), 7.60-7.77 (4H, m), 7.82-7.90 (1H, m), 8.00-8.04 (1H, m), 8.16-8.21 (2H, m), 8.50 (1H, br).

ESI-MS (m/e): 414 (M+H)+.

Example 158



[6-(2-fluoro-6-(methane sulfonamide) phenoxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine

The compound of Example 158 was produced using N-(2,3-difluorophenyl) methane sulfon amide, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR (CDCl3) δ : 3.04 (3H, s), 3.85 (3H, s), 6.83 (1H, d, J = 2.3 Hz), 7.01-7.03 (1H, m), 7.26-7.28 (1H, m), 7.36 (1H, d, J = 2.3 Hz), 7.45 (1H, d, J = 8.5 Hz), 7.58-7.60 (1H, m), 7.79 (1H, d, J = 2.3 Hz), 8.03 (1H, d, J = 8.5 Hz), 8.68 (1H, s).

ESI-MS (m/e): 429 (M+H)+.

Pharmacological test example carried out using compounds in accordance with this invention as test compounds is shown below.

Pharmacological test example 1: glucokinase activation action

Using compounds in accordance with this invention, glucokinase activation ability was measured.

The measurement of excellent glucokinase activation action of compound represented by the aforesaid formula (I) can be carried out by a process in accordance with literature (for example Diabetes, vol.45, pp.1671-1677, 1996) or a process in accordance with this.

The glucokinase activity was not directly measured using glucose-6-phosphoric acid, but the amount of Thio-NADH was measured which is formed when reporter enzyme glucose-6-phosphoric acid dehydrogenase produces phospho gluconolactone from glucose-6-phosphoric acid, and thereby degree of activation of glucokinase examined.

Recombinant human liver GK used in this assay is expressed in E.coli as FLAG fusion protein and refined with ANTIFLAG M2 AFFINITY GEL (Sigma).

The assay was carried out at 30°C using flat bottom 96-well plate. The assay buffer (25 mM Hepes Buffer: pH=7.2, 2 mM MgCl2, 1 mM ATP, 0.5 mM TNAD, 1 mM dithiothreitol) was charged in aliquot of 69 μl and DMSO solution of compound or as control, DMSO 1 μl was added. Thereafter enzyme mixture (FLAG-GK, 20 U/ml G6PDH) 20 μl cooled in ice beforehand was added by pipette, and thereafter, the substrate 25 mM glucose 10 μl was added, and reaction was started (final glucose concentration = 2.5 mM).

After the start of reaction, increase of absorbance at 405 nm was measured for ten minutes every 30 seconds, and evaluation of compound was carried out using the increment for the first five minutes. FLAG-GK was added so that absorbance increment after five minutes became between 0.05-0.1 in the presence of 1 % DMSO.

OD value in each concentration of compound to be evaluated was measured with making the OD value with DMSO control 100 %. From OD value of each concentration, Emax (%) and EC50 (μM) were calculated, and it was used as index of GK activated ability of compound.

GK activation ability of compound in accordance with this invention was measured. The results thereof are shown in Table 5.

Table 5

GK activation ability of the compounds of this invention

Compound number	Emax (%)	EC50 (μM)
Example 1	1000	0.18
Example 22	860	0.08
Example 31	1050	0.09

As shown in the aforesaid Table 5, the compound in accordance with this invention has excellent GK activation ability using Emax and EC50 as index, and is useful in therapy and/or prevention of diabetes mellitus, diabetes mellitus complication or obesity.

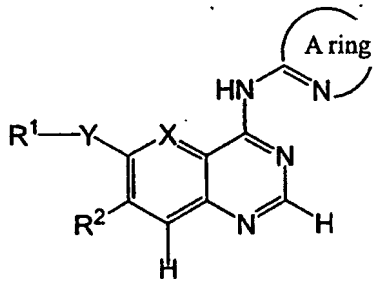
Possible Applications in Industry

In accordance with this invention, a novel substance having glucokinase activation action is put forward.

Substituted quinazoline represented by formula (I) or pyridopyrimidine derivative or a pharmacologically acceptable salt thereof put forward by this invention has excellent glucokinase activation action and is useful in therapy and/or prevention of diabetes mellitus, diabetes mellitus complication or obesity.

Patent Claims

1. A compound represented by formula (I) or the pharmacologically acceptable salts thereof



(I)

[wherein, X denotes a nitrogen atom or CH, Y denotes an oxygen atom or sulfur atom, and R^1 denotes an atom or a group arbitrarily selected from the following (1), (2), (3), (4), (5) and (6) (wherein, when R^1 is the following (1) to (5), is, and R^1 may contain the same or different 1-3 groups selected from the substituent group α),

(1) 5-6 membered heteroaryl group containing 1-3 heteroatoms selected from the group comprising a nitrogen atom, sulfur atom and oxygen atom in ring (said heteroaryl group may form a condensed ring with phenyl group),

(2) aryl group,

(3) straight or branched chain lower alkyl group,

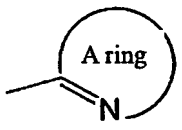
(4) 3-7C cycloalkyl group (one of carbon atom constituting the said group (except carbon atom bonding to Y) may be substituted by oxygen atom, NH, N-alkanoyl group or carbonyl oxy group),

(5) straight or branched chain lower alkenyl group,

(6) hydrogen atom

R^2 denotes a hydrogen atom or fluorine atom,

A ring is a monocyclic or bicyclic heteroaryl group represented by formula (II)



(II)

(the said heteroaryl group may contain one (sic, it must be one or more or one to some specific number) the same or different substituents selected from substituent group β)].

Substituent group α: lower alkyl group (the said lower alkyl group may be substituted 1-3 by halogen atom), 3-7C cycloalkyl group, lower alkoxy group, hydroxy group, hydroxyalkyl group (hydrogen atom of hydroxy group in said hydroxyalkyl group may be substituted by lower alkyl group), alkanoyl group, halogen atom, oxo group, lower alkyl sulphonyl group, lower alkyl sulfonyl amino group, mono- or di-lower alkylcarbamoyl group, mono- or di-lower alkylcarbamoyl alkyl group, mono- or di-lower alkyl sulphamoyl group, amino group, mono- or di-lower alkylamino group, cyano group, and 5-6 membered heteroaryl group which may contain 1-3 heteroatoms selected from the group comprising nitrogen atom, sulfur atom and oxygen atom in ring.

Substituent group β: lower alkyl group, lower alkoxy group, halogen atom, trifluoromethyl group, hydroxyalkyl group (hydrogen atom of hydroxy group in said hydroxyalkyl group may be further substituted by lower alkyl group), amino alkyl group (amino group in said amino alkyl group may be further substituted by lower alkyl group), alkanoyl group, carboxyl group, alkoxycarbonyl group and cyano group.

2. A compound or pharmacologically acceptable salts thereof in accordance with Claim 1, wherein R^1 is a group arbitrarily selected from the following (1), (2), (3) and (4) (wherein the said R^1 may contain the same or different 1-3 groups selected from the aforesaid substituent group α).

(1) 5-6 membered heteroaryl group containing 1-3 heteroatoms selected from the group comprising nitrogen atom, sulfur atom and oxygen atom in ring (the said heteroaryl group may form a condensed ring with phenyl group),

(2) aryl group,

(3) straight or branched chain lower alkyl group,

(4) 3-7C cycloalkyl group (one of carbon atom constituting the said group (except carbon atom bonding to Y) may be substituted by oxygen atom, NH, N-alkanoyl group or carbonyl oxy group).

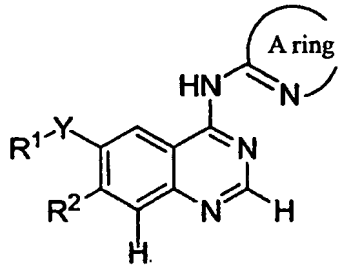
3. A compound or pharmacologically acceptable salts thereof in accordance with Claim 1, wherein R^1 is a group arbitrarily selected from the following (1) and (2) (wherein the said R^1 may contain the same or different 1-3 groups selected from the aforesaid substituent group α),.

(1) 5-6 membered heteroaryl group containing 1-3 heteroatoms selected from the group

comprising nitrogen atom, sulfur atom and oxygen atom in ring (the said heteroaryl group may form a condensed ring with phenyl group),
(2) aryl group.

4. A compound or pharmacologically acceptable salts thereof in accordance with Claim 3, wherein A ring is a thiazolo [5,4-b] pyridinyl group, pyrazinyl group, thiadiazolyl group or pyrazolyl group which may contain the same or different 1-3 substituents selected from the substituent group β.

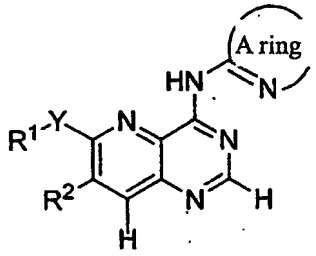
5. A compound or pharmacologically acceptable salts thereof in accordance with any one of Claim 3 or 4, wherein formula (I) is formula (I-1)



(I-1)

(wherein each symbol is the same as above).

6. A compound or pharmacologically acceptable salts thereof in accordance with any one of Claim 3 or 4, wherein formula (I) is formula (I-2)



(I-2)

(wherein each symbol is the same as above).

7. A compound or pharmacologically acceptable salts thereof in accordance with Claim 5, wherein Y is an oxygen atom,.

8. A compound or pharmacologically acceptable salts thereof in accordance with Claim 6, wherein Y is a sulfur atom,.

9. A compound or pharmacologically acceptable salts thereof in accordance with Claim 1, wherein the compound represented by formula (I) is
[6-(4H-[1,2,4] triazol-3-yl sulphanyl]-quinazolin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine,
[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-thiazol-2-yl-amine,
[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-pyrazine-2-yl-amine,
(6-phenoxy quinazolin-4-yl).-pyrazine-2-yl-amine,
[6-(4H-[1,2,4]), triazol-3-yl sulphanyl)-quinazolin-4-yl]-pyrazine-2-yl-amine,
[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine,
(6-phenoxy-quinazolin-4-yl).-thiazolo [5,4-b] pyridine-2-yl-amine,
[6-(2-fluoro-phenoxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine,
[6-(1-methyl-1H-imidazol-2-yl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine,
[6-(pyridin-2-yl sulphanyl)-quinazoline-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine,
[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-(3-methyl-[1,2,4] thiadiazol-5-yl-amine),
[6-[pyrimidin-2-yl sulphanyl]-quinazolin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine,
[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine,
[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-thiazolo .[4,5-b] pyrazine-2-yl-amine,
Benzthiazol-2-yl-[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-amine,
[6-(3H-[1,2,3] triazol-4-yl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine,
(1-methyl-1H-pyrazol-3-yl)-[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-amine,
[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-pyrimidine-4-yl-amine,
(5-methyl-pyrazine-2-yl)-[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-amine,
[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-pyridine-2-yl-amine,

(5-chloro-thiazol-2-yl)-[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-amine,
[6-(2-fluoro-1-fluoromethyl-ethoxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine,
(6-isopropoxy-quinazolin-4-yl)-pyradine-2-yl-amine,
(6-isopropoxy-quinazolin-4-yl).-thiazolo [5,4-b] pyridine-2-yl-amine,
[6-(2-hydroxy-(1S)-methyl-ethoxy-quinazolin-4-yl)]-thiazolo [5,4-b] pyridine-2-yl-amine,
(6-cyclopentyl oxy-quinazolin-4-yl)-thiazolo [5,4-b] pyridine-2-yl-amine,
[6-(2-fluoro-1-fluoromethyl-ethoxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
[6-(2-fluoro-1-fluoromethyl-ethoxy)-quinazolin-4-yl]-isoxazol-3-yl-amine,
[6-(2-fluoro-1-fluoromethyl-ethoxy)-quinazolin-4-yl]-(5-fluoro-thiazolo [5,4-b] pyridine-2-yl)-amine,
[6-(2-fluoro-1-fluoromethyl-ethoxy)-quinazolin-4-yl]-(5-methoxy-thiazolo [5,4-b] pyridine-2-yl)-amine,
[6-(4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine,
(6-phenoxy-pyrido [3,2-d] pyrimidine-4-yl)-thiazol-2-yl-amine,
[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-thiazol-2-yl-amine,
[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine,
[6-(5-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine,
Thiazolo [5,4-b] pyridine-2-yl-[6-(3H-[1,2,3] triazol-4-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-amine,
(6-methoxy-quinazolin-4-yl)-pyrazine-2-yl-amine,
(6-hydroxy-quinazolin-4-yl)-thiazolo [5,4-b] pyridine-2-yl-amine,
6-(1-methylpyrazol-3-yl sulphanyl)-thiazolo [5,4-b] pyridin-2-yl pyrido [3,2-d] pyrimidine-4-yl-amine,
(6-ethyl sulphanyl)-thiazolo [5,4-b] pyridin-2-yl pyrido [3,2-d] pyrimidine-4-yl-amine,
(5-methoxymethyl-1,2,4-triazol-3-yl sulphanyl) thiazolo [5,4-b] pyridin-2-yl pyrido [3,2-d] pyrimidine-4-yl-amine,
(5-methylpyrazine-2-yl).-6-(1,2,4-triazol-3-yl sulphanyl) pyrido [3,2-d] pyrimidine-4-

yl-amine,
6-(1-methyl imidazol-2-yl sulphanyl)-(5-methylpyrazine-2-yl) pyrido [3,2-d] pyrimidine-4-yl-amine,
6-(imidazol-2-yl sulphanyl)-(5-methylpyrazine-2-yl) pyrido [3,2-d] pyrimidine-4-yl-amine,
6-(1-ethylimidazol-2-yl sulphanyl)-(5-methylpyrazine-2-yl) pyrido [3,2-d] pyrimidine-4-yl-amine,
(5-methylpyrazine-2-yl)-6-(1-methylpyrazol-3-yl sulphanyl) pyrido [3,2-d] pyrimidine-4-yl-amine,
6-(1,5-dimethylimidazol-2-yl sulphanyl)-(5-methylpyrazine-2-yl) pyrido [3,2-d] pyrimidine-4-yl-amine,
6-(4-methyl imidazol-2-yl sulphanyl)-(5-methylpyrazine-2-yl) pyrido [3,2-d] pyrimidine-4-yl-amine,
(5-methylpyridine-2-yl)-6-(1,2,4-triazol-3-yl sulphanyl) pyrido [3,2-d] pyrimidine-4-yl-amine,
(5-fluoropyridine-2-yl)-6-(1,2,4-triazol-3-yl sulphanyl) pyrido [3,2-d] pyrimidine-4-yl-amine,
[6-(pyridin-2-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine,
[6-(1,3,4-thiadiazol-2-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine,
[6-(1-methyl-1H-tetrazol-5-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine,
[6-(4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-3-methyl-[1,2,4] thiadiazol-5-yl-amine,
[6-(4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]- (1-methyl-1H-pyrazol-3-yl)-amine,
(6-(3-fluoro-benzonitrile-2-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-3-methyl - [1,2,4] thiadiazol-5-yl-amine,
[6-(3H-[1,2,3] triazol-4-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]- (1-methyl-1H-pyrazol-3-yl)-amine,
[6-(5-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
[6-(3-chloro-pyridin-2-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]- (1-methyl-1H-pyrazol-3-yl)-amine,

[6-(3-cyano-pyridin-2-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]- (1-methyl-1H-pyrazol-3-yl)-amine,
[6-(3-amide-pyridin-2-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]- (1-methyl-1H-pyrazol-3-yl)-amine,
6-(1H-benzimidazol-2-yl sulphanyl)-N-(1-methyl-1H-pyrazol-3-yl) pyrido (3,2-d) pyrimidine-4-yl-amine,
6-[(5-amino-4H-1,2,4-triazol-3-yl) sulphanyl]-N-(1-methyl-1H-pyrazol-3-yl) pyrido (3,2-d) pyrimidine-4-yl-amine,
N-pyrazine-2-yl-6-(4H-1,2,4-triazol-3-yl sulphanyl) pyrido (3,2-d) pyrimidine-4-yl-amine,
N-isoxazol-3-yl-6-(4H-1,2,4-triazol-3-yl sulphanyl) pyrido (3,2-d) pyrimidine-4-yl-amine,
6-{[6-(4H-1,2,4-triazol-3-yl sulphanyl) pyrido [3,2-d] pyrimidin-4-yl] amino} nicotino nitrile,
(4-methyl-1,3-thiazol-2-yl)-6-(4-methyl-1,2,4-triazol-3-yl sulphanyl)-quinazoline-4-yl-amine,
(5-methyl-1,3-thiazol-2-yl)-6-(4-methyl-1,2,4-triazol-3-yl sulphanyl)-quinazoline-4-yl-amine,
6-(methyl benzoate-2-yl) sulphanyl-thiazolo [5,4-b] pyridin-2-yl quinazoline-4-yl-amine,
6-(2-hydroxymethyl phenyl sulphanyl)-thiazolo [5,4-b] pyridin-2-yl quinazoline-4-yl-amine,
6-(pyrazin-2-yl sulphanyl)-thiazolo [5,4-b] pyridin-2-yl quinazoline-4-yl-amine,
6-(3-fluoropyridin-2-yl sulphanyl)-thiazolo [5,4-b] pyridin-2-yl quinazoline-4-yl-amine,
6-(benzoate-2-yl sulphanyl)-thiazolo [5,4-b] pyridin-2-yl quinazoline-4-yl-amine,
6-(3-chloropyridin-2-yl sulphanyl)-(1-methylpyrazol-3-yl) quinazoline-4-yl-amine,
[6-(2-dimethylamino-ethyl sulphanyl)-quinazoline-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine,
[6-(cyclopentyl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine,
[6-(2-fluorophenyl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine,
[6-(2-methoxyphenyl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine,
[6-(3-chloropyridine-2-yloxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine,
[6-(3-cyanopyridine-2-yloxy)-quinazoline-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine,
[6-(3-carboxamide pyridine-2-yloxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine,

[6-(pyridine-2-yloxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine,
[6-(3-methylpyridine-2-yloxy)-quinazoline-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine,
[6-(methylcarbamoyl-methyl oxy)-quinazoline-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine,
[6-(3-methylsulfonyl pyridine-2-yloxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine,
[6-(3-chloropyridine-2-yloxy)-quinazolin-4-yl]-3-methyl-[1,2,4] thiadiazol-5-yl-amine,
[6-(3-fluoropyridine-2-yloxy)-quinazolin-4-yl]-3-methyl-[1,2,4] thiadiazol-5-yl-amine,
[6-(3-chloropyridine-2-yloxy)-quinazolin-4-yl]-pyridine-2-yl-amine,
[6-(tetrahydro-2H-pyran-4-yloxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
[6-(3,5-difluoro pyridine-2-yloxy)-quinazoline-4-yl]-3-methyl-[1,2,4] thiadiazol-5-yl-amine,
[6-(2-chloro-6-(methylsulfonyl) phenoxy)-quinazolin-4-yl]- (1-methyl-1H-pyrazol-3-yl)-amine,
[6-(2,4-difluoro phenoxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
[6-(2-fluoro-6-(5-methyl-[1,2,4] oxadiazol-3-yl) phenoxy)-quinazolin-4-yl]-3-methyl-[1,2,4] thiadiazol-5-yl-amine,
[6-(2-fluoro-4-(methylsulfonyl phenoxy)-quinazolin-4-yl]-3-methyl-[1,2,4] thiadiazol-5-yl-amine,
[6-(2-fluoro-6-(methylsulfonyl) phenoxy)-quinazolin-4-yl]- (1-methyl-1H-pyrazol-3-yl)-amine,
[6-(2-fluoro-6-(methylsulfonyl) phenoxy)-quinazoline-4-yl]- (1-ethyl-1H-pyrazol-3-yl)-amine,
[6-(2-fluoro-6-(methylsulfonyl) phenoxy)-quinazoline-4-yl]-pyrazine-2-yl-amine,
[6-(2-chloro-6-(methanesulphonyl amino) phenoxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
3-fluoro-2-({4-[[pyrazin-2-yl] amino] quinazolin-6-yl} oxy) benzonitrile,
[6-(butyl lactone-2-yloxy)-quinazoline-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
[6-(2,4-difluoro-6-(methylsulfonyl) phenoxy)-quinazoline-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
[6-(2-fluoro-6-(methylsulfonyl) phenoxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine,
N-(1-methyl-1H-pyrazol-3-yl)-6-[2-(methylsulfonyl) phenoxy] quinazoline-4-yl-amine,
3-fluoro-2-({4-[[5-methylpyrazin-2-yl] amino] quinazolin-6-yl) oxy) benzonitrile,
6-(3-chloropyridin-2-yl sulphanyl)-(1-methylpyrazol-3-yl) quinazoline-4-yl-amine,

6-(3-chloropyridin-2-yl sulphanyl)-(5-methyl-pyrazine-2-yl) quinazoline-4-yl-amine,
6-(3-chloropyridin-2-yl sulphanyl)-(1H-pyrazol-3-yl) quinazoline-4-yl-amine,
6-(acetyl piperidine-4-yl) oxy-N-[1,3] thiazolo [5,4-d] pyridin-2-yl quinazoline-4-yl-amine,
N-(1-methyl-1H-pyrazol-3-yl)-6-(pyrazine-2-yloxy) quinazoline-4-yl-amine,
N-(1-methyl-1H-pyrazol-3-yl)-6-(pyrimidine-4-yloxy) quinazoline-4-yl-amine,
6-[2-fluoro-1-(fluoromethyl) ethoxy]-N-[1,3] thiazolo [5,4-d] pyrimidin-2-yl quinazoline-4-yl-amine,
6-[(3-chloropyridine-2-yl) oxy]-N-1,3-thiazol-2-yl quinazoline-4-amine (1-methylpyrazol-3-yl) quinazoline-4-yl-amine,
6-(1,3-benzothiazol-2-yloxy)-N-(1-methyl-1H-pyrazol-3-yl) quinazoline-4-yl-amine,
N-(1-methyl-1H-pyrazol-3-yl)-6-(quinazoline-2-yloxy) quinazoline-4-yl-amine,
6-[(5-fluoropyridine-2-yl) oxy]-N-(1-methyl-1H-pyrazol-3-yl) quinazoline-4-yl-amine,
6-[(3-chloropyridine-2-yl) oxy]-N-(5-methyl-1H-pyrazol-3-yl) quinazoline-4-yl-amine,
N-(1-methyl-1H-pyrazol-3-yl)-6-(pyridine-3-yloxy) quinazoline-4-yl-amine,
6-[(3-chloropyridine-2-yl) oxy]-N-4H-[1,2,4]-triazol-3-yl quinazoline-4-yl-amine,
6-[(5-fluoropyridine-3-yl) oxy]-N-(1-methyl-1H-pyrazol-3-yl) quinazoline-4-yl-amine,
6-[(3-chloropyridine-2-yl) oxy]-N-[1,2,4]-thiadiazole-5-yl quinazoline-4-yl-amine,
N-(1-methyl-1H-pyrazol-3-yl)-6-[(3-methylpyridine-2-yl) oxy] quinazoline-4-yl-amine,
6-{[3-(difluoromethyl) pyridin-2-yl] oxy}-N-(1-methyl-1H-pyrazol-3-yl) quinazoline-4-yl-amine,
N-(1-methyl-1H-pyrazol-3-yl)-6-{[3-(trifluoromethyl) pyridin-2-yl] oxy} quinazoline-4-yl-amine,
[2-({4-[[1-methyl-1H-pyrazol-3-yl] amino] quinazolin-6-yl} oxy) pyridin-3-yl] methanol,
6-{[3-(fluoromethyl) pyridin-2-yl] oxy}-N-(1-methyl-1H-pyrazol-3-yl) quinazoline-4-yl-amine,
1-[2-({4-[[1-methyl-1H-pyrazol-3-yl] amino] quinazolin-6-yl} oxy) pyridine 3-yl] ethanone,
5-chloro-2-methyl-4-({4-[[1-methyl-1H-pyrazol-3-yl] amino] quinazolin-6-yl} oxy) pyridazine-3 (2H)-one,
6-[(6-fluoropyridine-2-yl) oxy]-N-(1-methyl-1H-pyrazol-3-yl) quinazoline-4-yl-amine,
[3-fluoro-2-({4-[[1-methyl-1H-pyrazol-3-yl] amino] quinazolin-6-yl} oxy) phenyl] methanol,
6-[2-fluoro-6-(fluoromethyl) phenoxy]-N-(1-methyl-1H-pyrazol-3-yl) quinazoline-4-yl-

amine,
[3-chloro-4-({4-[[1-methyl-1H-pyrazol-3-yl] amino] quinazolin-6-yl} oxy) phenyl] methanol,
Methyl-5-(methylsulfonyl)-2-({4-[[3-methyl-[1,2,4]-thiadiazol-5-yl] amino] quinazolin-6-yl} oxy) benzoate,
3-fluoro-2-({4-[[1-pyridine-2-yl-1H-pyrazol-3-yl] amino] quinazolin-6-yl} oxy) benzonitrile,
1-[3-fluoro-2-({4-[[1-methyl-1H-pyrazol-3-yl] amino] quinazolin-6-yl} oxy) phenyl] ethanone,
6-[(3-chloropyridine-2-yl) oxy]-N-[1-(difluoromethyl)-1H-pyrazol-3-yl] quinazoline-4-yl-amine,
3-chloro-N,N-dimethyl-2-({4-[[3-methyl-[1,2,4]-thiadiazol-5-yl] amino] quinazolin-6-yl} oxy) benzenesulphon amide,
6-[2-chloro-6-(ethylsulfonyl) phenoxy]-N-(3-methyl-1,2,4-thiadiazol-5-yl) quinazoline-4-yl-amine,
6-[2-fluoro-6-(methylsulfonyl) phenoxy]-N-(5-methylpyrazine-2-yl) quinazoline-4-yl-amine,
6-[2-chloro-6-(cyclopropyl sulfonyl) phenoxy]-N-(1-methyl-1H-pyrazol-3-yl) quinazoline-4-yl-amine,
6-[2-fluoro-6-(methylsulfonyl) phenoxy]-N-1H-pyrazol-3-yl quinazoline-4-yl-amine,
6-[3-cyclopropyl pyridin-2-yl] oxy]-N-(1-methyl-1H-pyrazol-3-yl) quinazoline-4-yl-amine,
[2-({4-[(1-methyl-1H-pyrazol-3-yl) amino] quinazolin-6-yl} oxy)-3-(trifluoromethyl) phenyl] methanol,
6-[2-fluoro-6-(methylsulfonyl) phenoxy]-N-pyridazin-3-yl quinazoline-4-yl-amine,
N-(5-chloropyrazine-2-yl)-6-[2-fluoro-6-(methylsulfonyl) phenoxy] quinazoline-4-yl-amine,
[3,5-difluoro-4-({4-[(1-methyl-1H-pyrazol-3-yl) amino] quinazolin-6-yl} oxy) phenyl] methanol,
3-fluoro-2-({4-[(1-methyl-1H-pyrazol-5-yl) amino] quinazolin-6-yl} oxy) benzonitrile,
6-[4-methyl-2-(methylsulfonyl) phenoxy]-N-(1-methyl-1H-pyrazol-3-yl) quinazoline-4-yl-amine,
6-(2,6-difluoro phenoxy)-N-(1-methyl-pyrazol-3-yl) quinazoline-4-yl-amine,
1-[3-methyl-2-([4-[(1-methyl-pyrazol-3-yl) amino] quinazolin-6-yl] oxy) phenyl] ethanone,

6-[2-(fluoromethyl)-6-(methylsulfonyl) phenoxy]-N-(1-methyl-pyrazol-3-yl) quinazoline-4-yl-amine,
3-methyl-2-({4-[(1-methyl-pyrazol-3-yl) amino] quinazolin-6-yl} oxy) benzonitrile,
Cyclopropyl [3-fluoro-2-([4-[{1-methyl-pyrazol-3-yl} amino] quinazolin-6-yl] oxy) phenyl] methanone,
6-[2-fluoro-6-(methoxymethyl) phenoxy]-N-(1-methyl-pyrazol-3-yl) quinazoline-4-yl-amine,
[6-(5-chloro-3-fluoropyridine-2-yloxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
[6-(3-fluoropyridine-2-yloxy)-quinazoline-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
6-[2-methyl-6-(methylsulfonyl) phenoxy]-N-(1-methyl-pyrazol-3-yl) quinazoline-4-yl-amine,
6-[2-(fluoromethyl)-6-(methylsulfonyl) phenoxy]-N-(1H-pyrazol-3-yl) quinazoline-4-yl-amine or
[6-(2-fluoro-6-(methane sulfonamide) phenoxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine.

10. A medicinal composition used for therapy, prevention and/or delay of onset of type II diabetes, containing following (i), (ii) and (iii).
(i) Compound in accordance with any of Claims 1-9 or pharmacologically acceptable salts thereof
(ii) At least one selected from the group comprising following (a)-(g),
(a) other glucokinase activator,
(b) biguanide,
(c) PPAR agonist,
(d) insulin,
(e) somatostatin,
(f) α-glucosidase inhibitor,
(g) insulin secretion accelerating agent.
(iii) Pharmacologically acceptable carrier.

11. A glucokinase activator comprising as an effective ingredient, a compound in accordance with any of aforesaid 1-10 or pharmacologically acceptable salts thereof.

12. A therapeutic and/or preventive agent of diabetes comprising as an effective

ingredient, a compound in accordance with any of aforesaid 1-10 or pharmacologically acceptable salts thereof.

13. A therapeutic and/or preventive agent of obesity comprising as an effective ingredient, a compound in accordance with any of aforesaid 1-10 or pharmacologically acceptable salts thereof.

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